DISSERTATION ON

THE EFFECT OF DEXAMETHASONE CYCLOPHOSPHAMIDE PULSE THERAPY IN COLLAGEN VASCULAR DISEASES

This dissertation is submitted to

THE TAMILNADU DR. M. G. R. MEDICAL UNIVERSITY

In partial fulfilment of the requirement of the award for the degree of

M.D BRANCH XX

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DECLARATION

I solemnly declare that the dissertation titled**, 'EFFECT OF DEXAMETHASONE CYCLOPHOSPHAMIDE PULSE THERAPY IN COLLAGEN VASCULAR DISORDERS'** was done by me at **Stanley Medical College and Hospital during 2009-2012** under the guidance and supervision of my **Chief ProfDr. K. Manoharan, M.D., D.D**

The dissertation is submitted to **THE TAMILNADU DR.M.G.R.MEDICAL UNIVERSITY** towards the partial fulfilment of requirement for the award **of M.D. Degree (Branch XX) in DERMATOLOGY, VENEREOLOGY & LEPROSY.**

Place:

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CERTIFICATE

This is to certify that the dissertation titled**'EFFECT OF DEXAMETHASONE CYCLOPHOSPHAMIDE PULSE THERAPY IN COLLAGEN VASCULAR DISEASES'**is submitted by **Dr. NITHYA.D**toThe TamilnaduDr. M. G. R Medical University, Chennai in partial fulfilment of the requirement of the award for the degree of**M.D BRANCH XX (DERMATOLOGY, VENEREOLOGY AND LEPROSY)** and is a bonafide work done by her under direct supervision and guidance.

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CONTENTS

INTRODUCTION

Collagen vascular diseases like Systemic Lupus Erythematosus (SLE) and Systemic Sclerosis (SSc) are always a challenge to the treating dermatologists. Though complete cure remains an enigma, therapeutic advances have aimed at inducing quick remission and improving the quality of life of the patients.

Pulse therapy is administration of single or multiple daily infusions of suprapharmacological doses of drugs to achieve a desired therapeutic effect. It is otherwise called as the "big shot ".[1]The history of pulse therapy began in 1969 when Kountz and Cohn introduced methylprednislone pulse therapy to prevent renal graft rejection.[2]

The monumental success of Dexamethasone Cyclophosphamide pulse therapy (DCP) in autoimmune bullous diseases (eg.Pemphigus) reported by Pasrischa et al., has prompted dermatologists to use DCP in collagen vascular diseases. [3]

Collagen vascular disorders are a group of diseases characterized by generalised alteration in connective tissue and have certain common features like autoimmunity, disordered cell mediated immunity, vascular abnormalities, arthralgia and skin disease.[4]

The diseases grouped under this category include lupus erythematosus, systemic sclerosis, localised and generalised morphoea, dermatomyositis, rheumatoid arthritis and Sjogren's syndrome.

Since the use of the first pulse therapy in collagen vascular disorders in 1976 for lupus nephritis, it has come a long way in improving the quality of life of patients. Now it is used in dermatomyositis, systemic sclerosis, mixed connective tissue disease and rheumatoid arthritis.

The long duration of steroid therapy required and the consequent effect on hypothalamo-pituitary axis (HPA) suppression with daily steroids makes pulse therapy, which is relatively free of such effects a welcome option in the therapeutic armamentarium of treatment of collagen vascular diseases.

Although success of pulse therapy in collagen vascular disease has been reported in the form of case reports, until the last decade there has not been any well documented clinical trials.

Documented success of DCP in collagen vascular diseases have come from Indian studies by Dhabai et al., published in 2005 that used DCP in SLE and by Ahmad et al who reported improvement in systemic sclerosis with DCP in 2003.[5,6]

This study aims at using Dexamethasone- Cyclophosphamide pulse therapy for systemic lupus erythematosus and systemic sclerosis since these are the most common collagen vascular diseases seen in our out patient department.

Also the novel aspect of this study is that the clinical improvement of dermatological manifestations will be based on well validated skin scoring systems.

AIMS & OBJECTIVES:

To study the efficacy of Dexamethasone –Cyclophosphamide pulse therapy in collagen vascular disorders.

1. To evaluate the degree of clinical and serological remission in Systemic Lupus Erythematosus and Systemic Sclerosis.
2. To evaluate the duration required to induce clinical remission.
3. To evaluate side effects of pulse therapy.

REVIEW OF LITERATURE

PULSE THERAPY- DEFINITION:

Pulse therapy is defined as "the administration of suprapharmacological doses of drugs in an intermittent manner to enhance the therapeutic effect and reduce the side effects."[1]

A wide number of drugs are used as pulse therapy in a wide variety of dermatological disorders. The most commonly used and most successful of them is Dexamethasone- Cyclophosphamide pulse (DCP) in Pemphigus vulgaris.

A sample list of other pulse therapies is:

DISEASE	PULSE THERAPY
Autoimmune blistering disease	Dexamethasone - Cyclophosphamide pulse Dexamethasone pulse Cyclophosphamide pulse Methyl prednisolone - Cyclophosphamide pulse Methyl prednisolone pulse Dexamethasone - Azathioprine pulse
Collagen vascular diseases	Dexamethasone - Cyclophosphamide pulse Cyclophosphamide pulse Methyl prednisolone – Cyclophosphamide pulse

Psoriasis vulgaris[7]	Methotrexate weekly pulse
Vitiligo vulgaris[8]	Betamethasone oral mini pulse Cyclophosphamide pulse
Alopecia areata[9]	Dexamethasone pulse, Methylprednisolone pulse
Pyoderma gangrenosum[10]	Cyclophosphamide pulse, Dexamethasone - Cyclophosphamide pulse,
Air borne contact dermatitis[11]	Azathioprine weekly/ monthly pulse
Acne vulgaris[12]	Azithromycin pulse

GLUCOCORTICOID PULSE THERAPY:

In the context of corticosteroids, pulse therapy is defined as 'treatment with more than 250mg of prednisolone or its equivalent per day, for one or more days'.[13]

The first pulse therapy used in Collagen vascular disease was methylprednisolone in 1976 for lupus nephritis.[2]

RATIONALE FOR GLUCOCORTICOID PULSE THERAPY:

- The high dose of corticosteroids given as pulse therapy exerts an immediate and profound anti inflammatory effect. In comparison to oral glucocorticoids, pulse steroids have additional non genomic immediate effects which are responsible for the quicker onset of action.
- Hence there is a faster clinical recovery symptomatically, as well as the inflammatory damage is minimised.
- The clinical recovery after pulse therapy has known to last for3 weeks.
- The toxicity has been consistently less compared to daily oral steroids in a number of studies. A case control study has shown that pulse glucocorticoids are not associated with more osteopenia or osteoporosis compared to high dose oral glucocorticoid therapy. This was also proved in another study done in rheumatoid arthritis patients. The cosmetogenic and diabetogenic effects of pulse steroids are less severe.
- There is no prolonged suppressive effect on the hypothalamo pituitary adrenal (HPA) axis. Moreover pulse therapy helps in more rapid tapering of oral steroids when used concomitantly at the start of therapy.[1]
- Therefore the risk benefit ratio of pulse therapy in comparison to daily oral steroid therapy is high.

METHYL PREDNISOLONE Vs DEXAMETHASONE:

Methylprednisolone is an intermediate acting steroid with a plasma half life of 12-36 hours. It has low potency to cause sodium and water retention (glucocorticoid: mineralocorticoid effect is 6:1) compared to hydrocortisone.[1]It is given in the dose of 15-30mg/kg body weight/day or 500-1000mg/m^2 body surface area up to a maximum of 1g/day for 1-3 days.[14]

Dexamethasone is a fluorinated glucocorticoid. It is along acting agent with a plasma half life of 36-72 hours. It has negligible mineralocorticoid activity. Hence there is almost no sodium retaining tendency. It is given in a dose of 2-5mg/kg body weight for 3 days consecutively.[15]

There is no significant difference between the 2 drugs in terms of efficacy. But the cost factor plays a crucial role in deciding between the two drugs. In the Indian context, dexamethasone would be more preferable since the cost of dexamethasone pulse therapy is only Rs.1085/patient compared to Rs 3660/patient with methylprednisolone for each pulse. The cost ratio of dexamethasone: methylprednisolone is roughly 1: 3.

In cases of brain edema when a drug with lower mineralocorticoid activity is preferred, Dexamethasone scores over methylprednisolone.[1]

MECHANISM OF ACTION OF PULSE STEROIDS:

Glucocorticoids have 4 main actions: anti-inflammatory, antiproliferative, vasoconstrictive and immunosuppressive properties.[16]

In collagen vascular disease, the anti-inflammatory and immunosuppressive properties are the main modes of action.

The cellular effects of steroids are mediated by 2 mechanisms: genomic and non genomic.

GENOMIC EFFECTS:

For genomic effects, the glucocorticoid has to bind to its specific receptors which are located in the cytoplasm of cells called cytosolic glucocorticoid receptors (cGCR).

The cGCR is a complex of various heat shock proteins (hsp70 and hsp90) and has a zinc finger motif which is required for transcription.

The cGCR due to its interaction with various kinases like mitogen activated protein kinases (MAPK),immunophilins and co-chaperones such as p23 and src plays a role in cell signalling.

The steroid receptor complex then migrates to the nucleus together as a homodimer and bind to specific DNA sequences in the promoter region which are called glucocorticoid responsive elements (GRE). This activates transcription factors which can cause either the induction or inhibition of synthesis of specific regulator proteins.

TRANSACTIVATION: If there is an induction of synthesis due to binding of a positive GRE it is called transactivation. In a similar way, binding to a negative GRE can also lead to inhibition of transcription. In this way, various cytokines, chemokines and enzymes mediating inflammation and immune response are activated or inhibited.

TRANSREPRESSION: Here the steroid receptor monomers directly interact with transcription factors without involvement of GREs.

For example, steroids can induce synthesis of IκB which can decrease the amount of NF – κB, which is proinflammatory, thereby decreasing the levels of cytokines induced by NFκB like IL 1, IL 6 and TNF α.

The genomic action is a slow process taking hours or days to see changes even at the cellular and tissue level. The effects of pulse therapy are too rapid to be explained by genomic events.

NON GENOMIC EFFECTS:

This can be due to 3 modes of action.

1) cGCR mediated non genomic effects:

Binding of glucocorticoids to cGCR leads to a rapid intracellular signalling via MAPK and co-chaperone src as mentioned above.

2) Non specific non genomic effects:

This occurs at high glucocorticoid concentrations. Here the glucocorticoids intercalate into the cellular membranes, influencing cation transport across plasma membrane and increasing proton leak across the mitochondrial membrane.

The ultimate result is decreased calcium and sodium cycling across the plasma membrane of immune cells leading to rapid immunosuppression and reduction of inflammatory process.

3) Effects mediated by membrane bound glucocorticoids receptors:

GCR are also found on cell membrane and are called as mGCR. Activation of these receptors causes rapid induction of apoptosis and induction of lipomodulin which inhibits production of prostaglandins and leukotrienes.

Buttergeit et al modules of glucocorticoid effect[16]

1) At low concentrations – genomic events

2) At moderate concentrations – bind to mGCR leading to cross membrane signal transmission for genomic and non genomic intracellular events.

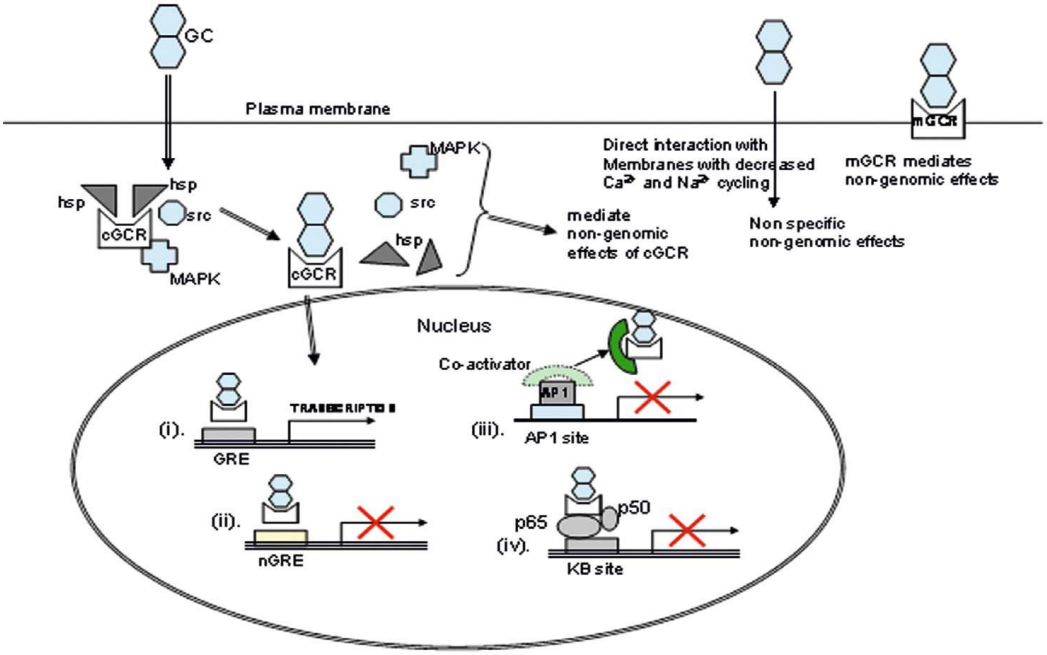
3) At high doses – steroids dissolve into the cell membrane and result in greater membrane stability.

Overall Glucocorticoid pulses causes

- Down regulation of activation of immune cells and proinflammatory cytokines leading to reduced expression of adhesion molecules and decreased neutrophil chemotaxis.
- These effects are similar to those seen with anti TNF α therapy.
- It was found that a single high dose will lead to 100% saturation of cytosolic receptors, but this receptor occupation reverts back quickly unless a new dose

is given. Hence single high doses do not have sustained effects and 3 day pulses are preferred.

MECHANISM OF ACTION OF GLUCOCORTICOIDS- Diagrammatic representation[3]



ADVERSE EFFECTS OF GLUCOCORTICOID PULSES:

Overall incidence of adverse effects may be low, partially because they allow more rapid tapering of oral glucocorticoid doses.[17]Complications due to large dose and route of administration are

1) Fluid overload

2) Hypertension - due to rapid flux in electrolytes

3) Neuropsychiatric symptoms – mood alteration, sleep disturbances, psychosis

- commonly seen in 10% of patients.

Rare complications:

1) Cardiac arrhythmias

It can also occur several days after therapy. It is due to rapid administration of large doses. Hence slow administration over 2 – 3 hours should be given.

2) Sudden death

3) Bradycardia – unrelated to speed and duration of infusion.

4) Intractable hiccups[44]

Others:

Hypokalemia, Hyperglycemia, Infections, Glaucoma, Cataract, Acne, diarrhoea, weakness, muscle pains, facial flushing, weight gain.

PRECAUTIONS:

Before starting therapy

1) Rule out systemic infection

Minor URI, skin infection and gastroenteritis are not a contraindication for therapy

2) Rule out malignant hypertension

Mild and moderate hypertension must be controlled by appropriate drugs.

During treatment

- Recording of heart rate(HR), respiratory rate (RR) and blood pressure(BP) every 15 – 30 minutes
- If arrhythmia is suspected, infusion is to be stopped immediately. ECG and serum electrolyte abnormalities are to be corrected.
- Estimation of blood sugar and electrolytes every alternate day.[1]

CYCLOPHOSPHAMIDE IN PULSE THERAPY

Cyclophosphamide is nitrogen mustard. It was first described by Arnold and Bourseaux. It is a widely used chemotherapeutic agent.

It is an alkylating agent widely used in cancer chemotherapy. It is a prodrug. In the liver it gets activated into two metabolically active compounds by cytochrome P450. The first compound 4-αhydroxycyclophosphamide is responsible for its anti cancer activity. Chloroacetaldehyde or aldophosphamide, the second metabolite produced by side chain oxidation is in turn converted into phosphoramide mustard (active), carboxyphosphoramide (inactive) and acrolein. Phosphoramide mustard is responsible for its immunosuppressive effects. Acrolein is the culprit metabolite behind haemorrhagic cystitis.[18]

The active principle- phospharamide mustard undergoes cyclization to a reactive aziridium intermediate, causes alkalinisation of guanosine bases of DNA resulting in cross linking of DNA, abnormal base pairing, imidazole ring cleavage with depurination and chain scission. This produces inhibition of DNA replication, leading to

cell death. It acts on both resting and dividing lymphocytes. On T cells, it specifically causes inhibition of suppressor Tcells than T helper cells. The effect on B cells is more prolonged since B cells take more time to recover from the suppression induced by an alkylating agent.

ADVERSE EFFECTS:

1. Haematological: It produces myelosuppression especially leucopenia. The nadir commonly develops 8-12 days after initiation of therapy. It is a dose limiting side effect. Thrombocytopenia and anaemia are less frequent.
2. Urological damage: Haemorrhagic cystitis is the most important urological complication. The principle metabolite producing this condition is acrolein. It also produces increased frequency, urgency, dysuria,microscopic hematuria, bladder telangiectasias, bladder fibrosis and vesicouretral reflux.
3. Gonadal damage: In males it causes azoospermia by depletion of testicular germ cells, whereas in females, disappearance of primordial follicles results in premature ovarian failure. The dose of cyclophosphamide required to produce gonadal failure is dependent on the age of the patient. For females, in their 20s, 30s, 40s, the cumulative dose required is 20, 10, 5 g respectively.[19]The benefits of using testosterone in males and leuprolide acetate in females to prevent gonadal failure are not fully known. Cryopreservation of reproductive material can be offered to patients if adequate resources are available.
4. Gastrointestinal toxicity: Nausea and vomiting are very common side effects. They can be easily controlled by antiemetics like ondansetron.

5. Carcinogenesis: Transitional cell carcinoma of renal pelvis, ureter and bladder, non-Hodgkin's lymphoma, acute leukaemias and squamous cell carcinomas can occur.[20]
6. Cutaneous toxicity: Anagen effluvium, hyper pigmentation of nails and skin, mucositis, acral erythema and persistent pigmented band over teeth are common complications.
7. Teratogenicity: If given in the first trimester of pregnancy.

   Pulse cyclophosphamide generally has less urological side effects compared to oral Cyclophosphamide because of ensurance of hydration in in-patients.

CONTRAINDICATIONS:

ABSOLUTE: Hypersensitivity.

RELATIVE:

Pregnancy

Lactation

Bone marrow suppression: Leucocytes less than 3000 cells/cubic mm, Platelet count less than 1 lakh cells/cubic mm.

Transitional cell carcinoma of bladder.[18]

Impaired hepatic/ renal functions.

PRECAUTIONS:

Ensure adequate hydration of 2-3 litters/day while on cyclophosphamide pulse therapy.

Before starting cyclophosphamide pulse rule out infections e.g. Latent Tuberculosis

DEXAMETHASONE –CYCLOPHOSPHAMIDE PULSE THERAPY:

Initially, only dexamethasone pulses were used. Cyclophosphamide boluses were added because relapses were frequent with dexamethasone alone. The combination of cyclophosphamide and dexamethasone has synergistic effect. This synergy is observed only with high dose cyclophosphamide and not with low doses.[21]The addition of cyclophosphamide improves the outcome of renal and pulmonary disease activity. In patients who are unmarried only I.V.dexamethasone with daily 50mg azathioprine without any bolus is given (DAP pulse).

PHASES OF PULSE THERAPY:

There are 4 phases in the Dexamethasone cyclophosphamide pulse therapy for collagen vascular diseases.

Phase I: 3 days of I.V. Dexamethasone (100 mg) in 500ml of 5% dextrose with I.V. Cyclophosphamide (500 mg) on the first day. Pulses are repeated once in 28 days. In between pulses only tablet cyclophosphamide 50mg is given. This phase lasts up to remission of the disease process (clinical or laboratory).

Phase II: Lasts up to 6 months after clinical remission

Phase III: Only 50mg oral cyclophosphamide is given for 1 year.

Phase IV: Follow up without any treatment for 2-3 years.

If there is any relapse of disease activity in phase II OR III, then the patient enters phase I again. The same regimen is followed in Pemphigus vulgaris, but the duration of phase II is 9 months.[22]

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

DEFINITION: A systemic disease characterised by multisystem organ inflammation, most commonly the skin, joints and vasculature, and associated immunological abnormalities. [23]

REVISED AMERICAN RHEUMATISM ASSOCIATION (ARA) CRITERIA FOR DIAGNOSIS OF SLE (1982)

1. Malar rash-

Fixed erythema, flat or raised over malar eminence, sparing the nasolabial fold.

2. Discoid rash-

Erythematous raised patches with adherent keratotic scaling & follicular plugging; atrophic scarring occurs in older lesions.

3. Photosensitivity-

Skin rash as a result of unusual reaction to sunlight, obtained by patient history or physician observation.

4. Oral ulcers-

Oral or nasopharyngeal ulcers; usually painless; observed by physicians.

5. Non erosive arthritis-

Non erosive arthritis involving two or more peripheral joints and is characterized by swelling or effusion.

6. Serositis-

Pleuritis: Convincing history of pleural pain, pleural rub or evidence of pleural effusion

Pericarditis- ECG, pericardial rub or evidence of pericardial effusion.

7. Renal disorder-

Persistent proteinuria of more than 0.5g/d or more than 3+;

Cellular casts in urine-RBC, Haemoglobin, granular, tubular or mixed casts.

8. Neurological disorder-

Seizures- in the absence of drugs, metabolic derangement, diabetic ketoacidosis (DKA), uremia or electrolyte imbalances.

Psychosis.

9. Haematological disorder-

Hemolytic anemia with reticulocytosis

Leucopenia: <4000c/mm on 2 or more occasions

Lymphopenia: <1500c/mm on 2 or more occasions

Thrombocytopenia: < 1 lakh c/mm in the absence of offending drugs

10. Immunological disorder-

Anti ds DNA antibodies

Anti Sm antibodies

Antiphospholipid and anticardiolipin antibodies, lupus anticoagulant.

False positive serological test for syphilis (STS) i.e. VDRL for more than 6months

11. Antinuclear antibodies-

Abnormal titers of ANA by immunofluorescence (IF) in the absence of drugs known to be associated with drug induced lupus syndrome.

Presence of 4 or more of the above criteria either simultaneously or sequentially is a pre requisite for diagnosis.

It is 96% sensitive & 96% specific.[23]

PATHOGENESIS OF SYSTEMIC LUPUS ERYTHEMATOSUS:

The basic pathology in SLE involves a complex interplay of host factors and environmental factors, leading to a loss in immune tolerance. This results in

production of auto antibodies directed against the patient's own nucleosomes and RNAs. The evolution of disease process consists of 4 phases

1. Susceptibility: The inherent HLA type, complement deficiencies, Gene polymorphism for TNF α increase the susceptibility of the individual.
2. Induction phase: Environmental factors lie V radiation, viruses , drugs and tobacco induce apoptosis and triggers antigen processing by dendritic cells.
3. Expansion phase: Stimulation of immune system results in Tcell expansion and B cell proliferation with the end result of autoantibody formation.
4. Injury phase: The ultimate end result is tissue damage caused by deposition of immune complexes and cytotoxic T cells along with release of numerous inflammatory mediators.[24]

The role of pulse therapy of dexamethasone and cyclophosphamide is at the level of expansion and injury phase. By the immunosuppressive potential both the drugs inhibit T cell proliferation resulting in decreased production of cytokines like TNF α, IFNα other inflammatory mediators. T cell mediated activation of auto reactive B cells is suppressed resulting in decreased production of auto antibodies.

CLINICAL EVALUATION OF SLE PATIENTS:

Objective evaluation of disease activity in Lupus Erythematosus can be done by various methods like CLASI, SLEDAI, and BILAG etc.[23]

CUTANEOUS LUPUS DISEASE AREA AND SEVERITY INDEX (CLASI)

Cutaneous Lupus Disease Area and Severity Index (CLASI) were developed in the Jefferson Medical College, Philadelphia[25]. It measures the cutaneous disease activity and residual damage separately.

The body surface is divided into 13 areas with increased weightage being given to the most commonly affected sites like the nose including malar area, ears, posterior neck and shoulder. The content validity of CLASI has been assessed by American College of Rheumatology and was found to be of adequate validity.

ADVANTAGES OF CLASI:

1. Disease activity and damage are scored separately. If on the other hand a cumulative score of the area affected would have been measured, it would have resulted in stable scores with scarring Lupus, although the activity may be decreasing.
2. Ease of administration.
3. Non reliance on invasive tests.

DISADVANTAGES OF CLASI:

1. It does not take into account the systemic disease activity which may not correlate with the cutaneous activity.
2. Other cutaneous lesions such as bullous lesions, livedoreticularis etc. are not included in the scoring.

CLASI SCORING

ANATOMICAL LOCATION	ERYTHEMA 0-Absent 1-Pink, faint 2-Red 3-Dark red/purple/crusted Hemorrhagic	SCALE/ HYPERTROPHY 0-Absent 1- Scale 2- Veruccous/ hypertrophic	DYSPIGMENTA-TION 0-Absent 1-Dyspigmentation.	SCARRING/ATROPHY / PANNICULITIS 0-Absent 1-Scarring 3-Severely atrophic scarring or panniculitis
Scalp				
Ears				
Nose(including malar area)				
Rest of face				
V area of neck				
Past. Neck& Shoulder				
Chest				
Abdomen				
Back, Buttocks				
Arms				
Hands				
Legs				
Feet				

MUCOUS MEMBRANE DYSPIGMENTATION

0-Absent 1-Lasts less than 12 m

1-Present2-Lasts more than 12 m

ALOPECIA

Recent Hair loss (within the last 30 days/as reported by patient)		Scarring	
0-No 1-YES		NB: if scarring and non-scarring aspects seem to coexist in one lesion, please score both	
ALOPECIA(clinically not obviously scarred)		Scarring of the scalp (judged clinically)	
0-absent 1-diffuse; non-inflammatory 2-focal or patchy in one quadrant; 3-focal or patchy in more than one quadrant		0- absent 3- in one quadrant 4- two quadrants 5- three quadrants 6- affects the whole skull	

Total Activity Score: Total Disability Score:

SYSTEMIC LUPUS ERYTHEMATOSUS DISEASE ACTIVITY INDEX (SLEDAI)

This is a complex scoring system taking into account systemic symptoms, cutaneous manifestations and laboratory parameters. Since this scoring also takes into account complement levels, such a scoring may not be possible in resource poor settings.[26]

LABORATORY MONITORING OF DISEASE ACTIVITY

Apart from usual parameters such as Erythrocyte sedimentation rate (ESR) and C- reactive protein, in SLE antidsDNA antibody levels and complement levels are known to correlate with disease activity.

Anti dsDNA test was incorporated in the 1982 revised American College of Rheumatology criteria for the diagnosis of SLE. Apart from diagnosis, it also aids in monitoring disease activity and determining the prognosis. The anti dsDNA antibodies can be eluted from experimental animals and human kidneys affected by lupus nephritis. Serum anti dsDNA levels is at high titres during proliferating lupus nephritis and they are more likely to play in role in its development.[27]

Recent reports also suggest anti dsDNA may have a role in neurological disease by its ability to bind to NR2 glutamate receptors inducing neuronal apoptotic death. But, there is a weak correlation with skin disease activity.[28] Also, the role of anti dsDNA in other clinical manifestations is not entirely studied.A high binding capacity is associated with poor prognosis.Anti dsDNA can be measured using various techniques such as the ELISA and immunofluorescence which are economical compared to the

Farr technique which measures the high avidity more pathogenic radio labelled anti dsDNA.

Antinuclear antibody levels do not correlate with disease activity.

SYSTEMIC SCLEROSIS

DEFINITION: It is a multisystem disorder characterized by the association of vascular abnormalities, connective tissue sclerosis and atrophy and auto antibodies.[29]

SUBCOMMITTEE OF SCLERODERMA CRITERIA OF THE AMERICAN RHEUMATISM ASSOCIATION

Major criteria:

Scleroderma proximal to the digits, affecting limbs, face, neck or trunk.

Minor criteria

a) Sclerodactyly
b) Digital pitted scars
c) Bilateral basal pulmonary fibrosis.

1 major and any 2 minor criteria should be present for diagnosis.

It has 97% sensitivity and 98% specificity.[29]

CLASSIFICATION OF SYSTEMIC SCLEROSIS:

DIFFUSE CUTANEOUS SYSTEMIC SCLEROSIS:

- Short interval (less than 1 year) between the onset of Raynaud's phenomenon and the development of skin changes.
- Truncal and peripheral skin involvement
- Tendon friction rubs
- Pulmonary fibrosis, renal failure, gastrointestinal disease, myocardial involvement.
- Capillary drop out visible in nail folds.
- Scl-70 antibodies.
- Anticentromere antibody negative.

LIMITED CUTANEOUS SYSTEMIC SCLEROSIS:

- Long history of Raynaud's phenomenon
- Limited skin involvement only
- Calcification, telangiectasia, late onset of pulmonary hypertension
- Capillary dilatation visible in nail folds without drop outs.
- Anticentromere antibody positivity.[30]

PATHOGENESIS OF SYSTEMIC SCLEROSIS:

Similar to SLE in scleroderma the host and environmental factors act in conjuncture to stimulate an autoimmune process and endothelial damage. One of the early events in the pathogenesis is an immunological trigger of T cells. Macrophages,

mast cells and platelets. These in turn elaborate various cytokines, adhesion molecules and growth factors which results in the expansion of fibrogenic clones of tissue fibroblasts. These clones of fibroblasts over express genes encoding for extracellular matrix components and behaves in a relatively autonomous way.[32]

The end result is an excessive deposition of collagen and other connective tissue matrix proteins within blood vessel wall resulting in vasculopathy (Raynaud's phenomenon), in the skin producing hide bound skin, mask like facies and difficult mouth opening and in the internal organs producing dysphagia, restrictive lung disease etc.

CLINICAL EVALUATION OF SYSTEMIC SCLEROSIS DISEASE ACTIVITY:

SKIN SCEROSIS MEASUREMENT:

The concept of using a skin score was first sowed by Farmer et al (1960) and Barnett et al (1969) who in their separate studies noted that extensive skin change was associated with major visceral involvement in SSc. Since then several studies have demonstrate that the outcome in scleroderma is associated with baseline skin score. The change in skin score reflects the severity of visceral involvement and determines the prognosis.

The most popular score was the Rodnan skin score (RSS) introduced in 1979. Here biopsies the skin thickness is measured from 26 sites by measuring the net weight and dry weight. The skin thickness was measured in grades from 0 to 4. It has undergone various modifications as follows:

22 site modified RSS (0 to 3, maximum 66) –Kahaleh et al in 1986

–10 site modified RSS (0 to 3, maximum 30) –Clements et al in 1990

–17 site modified RSS (0 to 3, maximum 51) –Clements et al in 1993

Modified Rodnan scoring now measures the skin score from 17 sites rather than 26. Skin thickness rather than tethering is assessed. Limited cutaneous disease and overlap syndromes can be especially challenging. Influence of co-morbidity including soft tissue swelling, loss of subcutaneous fat, skin oedema interferes with accurate assessment.

Durometry: It was first developed by Falanga and Bucalo in1993.

Elastometry: It was developed by Balbir-Gurman et al in 2002. It is a non-invasive measurement of biomechanical skin properties in systemic sclerosis.

Ultrasound: Ultrasound for measurement of skin thickness in scleroderma was first introduced by Moore TL et al in 2003.A seventeen-point dermal ultrasound scoring system was developed which is a reliable measure of skin thickness in patients with systemic sclerosis. It also has the advantage of being non invasive.[33]

HIDEBINDING/ TETHERING SKIN SCORE OF FURST et al:

In comparison to the Modified Rodnan skin score and other methods a rather simple scoring and dependent only on clinical findings and not on histopathology was developed by Furst et al.

0- Skin not tethered or bound down.

1- Mild tethering

2- Moderate tethering

3- Severe tethering

10 skin sites are examined which are the face, back, chest, abdomen, arms, forearms, hands, thighs, legs and feet. The sum total of all points at all sites is the skin score. The maximum score is 30.[34]

EVALUATION OF SYSTEMIC INVOLVEMENT:

The pulmonary function tests, radiological changes in HRCT like ground glass appearances have been used to measure lung involvement. Renal involvement is measured by serum creatinine, creatine clearance and 24 hour urine protein. Gastrointestinal involvement is assessed clinically by degree of dysphagia and by oesophageal manometry. Involvement of other systems like cardiac (ECG, echocardiogram) and musculoskeletal system (muscle enzymes) are also assessed.

PULSE THERAPY IN SYSTEMIC LUPUS ERYTHEMATOSUS & SYSTEMIC SCLEROSIS

The first pulse therapy in SLE was the use of methylprednisolone for lupus nephritis in 1976. Consequently methyl prednisolone pulse was used by Isenberg for recalcitrant cases of SLE. Methylprednisolone along with cyclophosphamide pulse therapy was studied by Hu J et al[35] and reported clinical remission after 8-10 pulses.

Dexamethasone along with cyclophosphamide in pulse therapy has been mainly used by Indian physicians. Dhabhai ET al[5] along with Garg et al reported cutaneous remission in most patients. Gupta ET al[36] used DCP in a single SLE patient and reported remission in 11 pulses. Sudip ET al[48] reported 75% improvement in all cutaneous manifestations by 4 pulses. Similar results were obtained by S Parajauliet al[37] in 5 patients.

The earliest documented evidence of pulse therapy in systemic sclerosis was in 1982 by Isenberg et al who used methyl prednisolone pulse therapy. Pulse therapy again came into prominence when Dexamethasone pulse was shown to produce remission in a 22 year old patient by J S Pasrischa et al in 1990.[38]Although there have been controversies regarding the precipitation of renal crisis by high dose steroids, it has been refuted in various Indian reports by Ramam B et al andPai BS et al.[39]

In a prospective study conducted by Ahmed et al, pulse therapy was shown to halt the disease progression when started early in the course of the disease with improvement in skin sclerosis, pulmonary function tests, ESR and histopathological examination of the skin.[6] None of the patients involved in his studied showed any relapse or reversal of the improvement achieved after being put of on pulse therapy.

Dexamethasone pulse therapy alone without cyclophosphamide was used by Pasricha *et al*., where he observed that around 12-21 pulses were needed to achieve clinical remission.[38] Similar studies conducted by Gupta et al and Ahmed et al recommend 12-18 pulses for clinical improvement.[39] They also observed that pulmonary functions improved with 4-6 pulses itself. Sharada *et al.* used a shorter duration of pulse therapy for 6 months and made an observation that such courses

produce clinical improvement of skin scores alone[40].Griffith evaluated the use of i.v. cyclophosphamide and methylprednisolone for 6 pulses and the modified rodnan skin scoring improved by 35%. Pakas et al observed that the effect of I.V cyclophosphamide in reducing skin score was significant when given along with high dose steroids[41]. Along with low dose steroids, the results obtained were not that significant.

Airo *et al*. used intravenous cyclophosphamide alone for active alveolitis for a period of six months and found that it produced significant improvement in pulmonary function tests. Barbara *et al*. performed a large scale study in 103 patients with alveolitis by administering i.v. as well as daily oral cyclophosphamide for 12-18 months and observed marked improvement of PFT[42]. Vatwani *et al*. used pulse therapy in a paediatric patient and observed that eight pulses of dexamethasone along with i.v. cyclophosphamide without oralcyclophosphamide is effective.[43]

Side effects peculiar to pulse therapy include hiccups[44], facial flushing[46], diarrhoea, weakness, generalized swelling and weight gain, joint and muscle pains. This was reported by Verma KK and Kanwar AJ et al. These side effects are usually observed with each pulse and last for a few days afterwards.Most patients are able to tolerate these symptoms and continue treatment[45].

MATERIALS AND METHODS

TYPE OF STUDY:

This is a type of open labelled non randomised prospective therapeutic study. Here the patients act as their own control.

SAMPLE SIZE:

A sample size of 36 patients was selected. Out of these, 20 patients had systemic lupus erythematosus and the other 16 had Systemic Sclerosis.

STUDY PLACE:

This study was conducted at the Department of Dermatology, Stanley Medical College in association with other departments for evaluation of systemic involvement.

STUDY PERIOD:

The study was conducted over a period of 2 years from November 2009 to October2011.

PATIENT SELECTION CRITERIA:

INCLUSION CRITERIA:

1. Systemic lupus erythematosus and systemic sclerosis patients diagnosed as per ARA criteria.
1. Age: 13 to 60 years.

2. Severe skin lesions not responding to high dose daily steroids
3. Presence of systemic involvement.

EXCLUSION CRITERIA:

1. Pregnancy.
2. Lactating mothers.
3. Children <12 years.
4. Ischemic heart disease.
5. Uncontrolled hypertension.
6. Active infections except Minor upper respiratory tract infections, acute gastroenteritis and skin infections.

PROCEDURE:

The patients were selected according to the inclusion criteria. A detailed history and physical examination was done. The following investigations were done prior to starting pulse therapy.

Diagnostic tests

Skin biopsy, ANA, Anti dsDNA

Tests to find out systemic involvement:

Renal: Blood urea, serum creatinine, urine routine & 24 hour urinary protein.

Cardiac: ECG, Echocardiogram.

Pulmonary: X ray chest, pulmonary function tests.

G.I: Barium swallow, OGD scopy.

CNS: EEG, CT scan brain.

Musculoskeletal: Creatine phosphokinase (CPK).

Hematological: Complete hemogram, platelet count, peripheral smear.

Tests to assess fitness for pulse therapy: Mantoux, blood sugar, pregnancy tests in females.

Informed consent & photographs.

ADMINISTRATION OF PULSE THERAPY:

The patients selected are hospitalised a day before the pulse therapy. Pre pulse investigations such as blood sugar, urea, serum creatinine, electrolytes, liver function tests, complete hemogram and urine routine are taken during each cycle. If all parameters are normal the pulse therapy is administered. Injection dexamethasone 100mg in 500ml of 5% dextrose by slow intravenous infusion over 2-3 hours is given for 3 consecutive days. On day 1, injection cyclophosphamide 500mg is also added. On rest of the days only tablet cyclophosphamide 50 mg per day is given. In young unmarried patients and those who have not completed their family only injection dexamethasone is given. On the rest of the days, oral azathioprine 50 mg per day is given. In patients with diabetes millets 8 U of regular Insulin was added into the 5% dextrose solution.

Pulse rate, blood pressure and ECG will be monitored before start of the infusion. Intermittent monitoring of pulse and blood pressure is done every half an hour during the infusions. The electrolytes and blood sugar are measured after the end of pulse therapy. If all parameters are normal the patient is discharged the next day.The next pulse is repeated after 28 days. In SLE patients in addition oral

chloroquine 250mg per day is given. In systemic sclerosis patients, vasodilators (nifedipine 10mg t.d.s) are given in all patients.

PRECAUTIONS:

- All patients were instructed to maintain a daily fluid intake of 2 L to prevent the development of hemorrhagic cystitis.
- Calcium supplements (1500mg/day) were given to all patients to prevent the development of osteoporosis
- During the 3 days of pulse therapy, potassium chloride syrup was given to minimise the risk of development of hypokalemia
- Ophthalmic examination was done before the start of therapy and every 6 months to rule out glaucoma and posterior sub capsular cataract.

EVALUATION OF RESPONSE:

In systemic lupus erythematosus, disease activity was evaluated by measuring

- CLASI score for cutaneous improvement,
- Clinical assessment of improvement in malar rash, photosensitivity, discoid rash, alopecia, oral erosions, fever, joint pain and symptoms pertaining to other system involvement.
- Laboratory monitoring of renal function tests including blood urea, serum creatinine and 24 hour urinary protein,
- Total and differential counts,
- Erythrocyte sedimentation rate (ESR)
- ANA titre

- Anti dsDNA titre

  In systemic sclerosis, disease activity was evaluated by measuring

- Skin tightening measurement using Hide binding/ tethering skin score of Furst et al
- Clinical evaluation of Raynaud's phenomenon, digital ulcers, pigmentary alterations
- Symptoms pertaining to other system involvement.
- Pulmonary function tests and renal function tests including blood urea, serum creatinine and 24 hour urinary protein
- ESR

RESULTS

IN SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS

A total of 20 SLE patients were recruited in the study group for pulse therapy. The results at the end of a minimum of 8 pulses is discussed

AGE DISTRIBUTION:

Of the twenty patients the youngest was 17 years old and the oldest was 34 years old. The highest number of patients (30%, 6 patients) were in the age group of 20-25 years. The mean age of the patients was 23.2 years. The age distribution is represented graphically in figure 1.

SEX DISTRIBUTION:

The study group included 19 females and 1 male, with a female: male ratio of I9:1.

DURATION OF ILLNESS:

The average duration of illness of the patients included in the study before pulse therapy could be initiated was 16.5 months. The shortest duration was 2 months in patient no.4 to 42 months in patient no.20.

CUTANEOUS MANIFESTATIONS

Only those patients who had skin manifestations were included in this study. The relative distribution of cutaneous features are: discoid rash in 100%, malar rash in

85% (17 patients), photosensitivity in 95% (19 patients), oral erosions in 90% (18 patients), and alopecia in 85%. Other manifestations seen were livedoreticularis in 1 patient (patient no.6) who also had neurological manifestations; bullous lesions seen in one patient (patient no.5) urticarial vasculitis in 1 patient (patient no.2) who had vasculitis retina and vasculitic ulcers were seen in 3 patients. The prevalence of skin manifestations is representated in figure 2.

CUTANEOUS LUPUS AREA AND SEVERITY INDEX (CLASI):

The activity score of CLASI, was between 12 and 34, out of a total score of 70 at the initiation of treatment. There was a fall in the CLASI activity scores in all the 20 patients at the end of 8 cycles of pulse therapy. The final CLASI activity score was 0 in 5 patients (25%). In 13 other patients (65%) the CLASI activity score recorded a marked fall to a score of less than 5. In 2 patients (10%) alone there was a score of more than 10.

The difference in the CLASI activity scores before the initiation of pulse therapy and after the completion of 8 pulses were analysed using the paired‘t’ test.

Standard deviation (S.D) = 5.785

Standard error of difference (S.E) = 1.294

The final t value was 17.85.

The probability of error (p value) for the given t values with a degree of freedom of 19 was less than 0.005.

Since the probability of error was very low ($p< 0.05$), the difference in the CLASI activity before and after the pulse therapy was statistically significant.

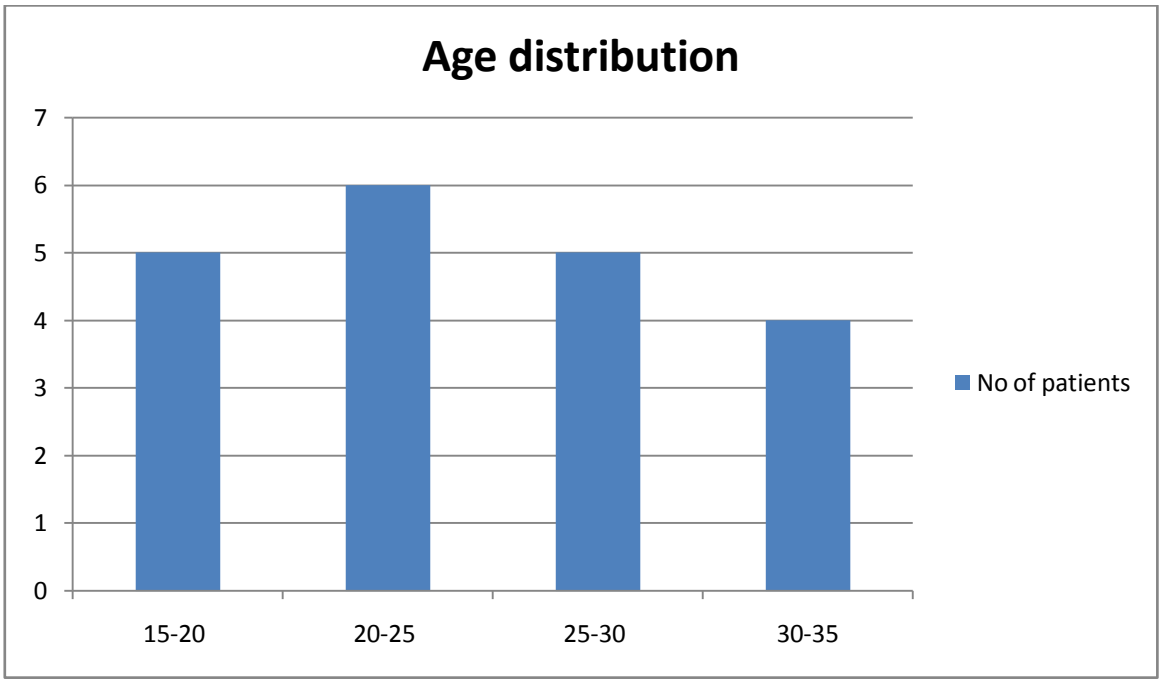


Figure 1

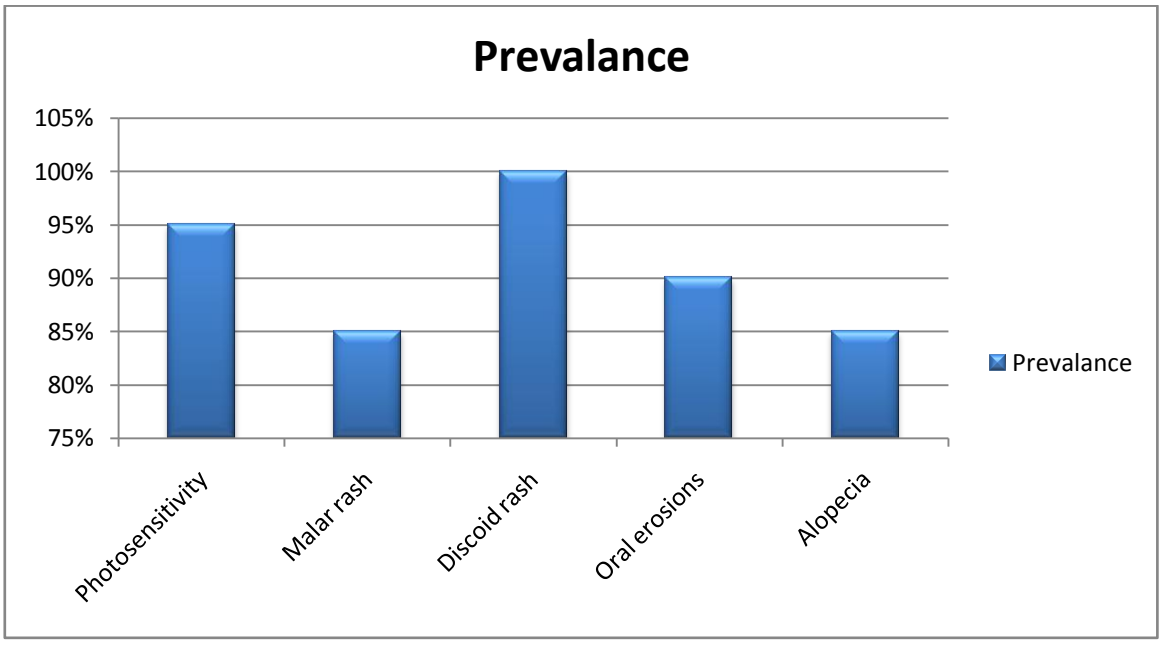


Figure 2

Whereas the activity score showed significant improvement in all but two patients, the damage score showed a different picture. The damage score which measures the residual dyspigmentation and scarring showed an initial increase in some patients as the disease activity subsided and the malar and discoid rashes left behind dyspigmentation and so did the mucosal erosions. The dyspigmentation took a long time to improve and seemed unrelated to the number of pulses.

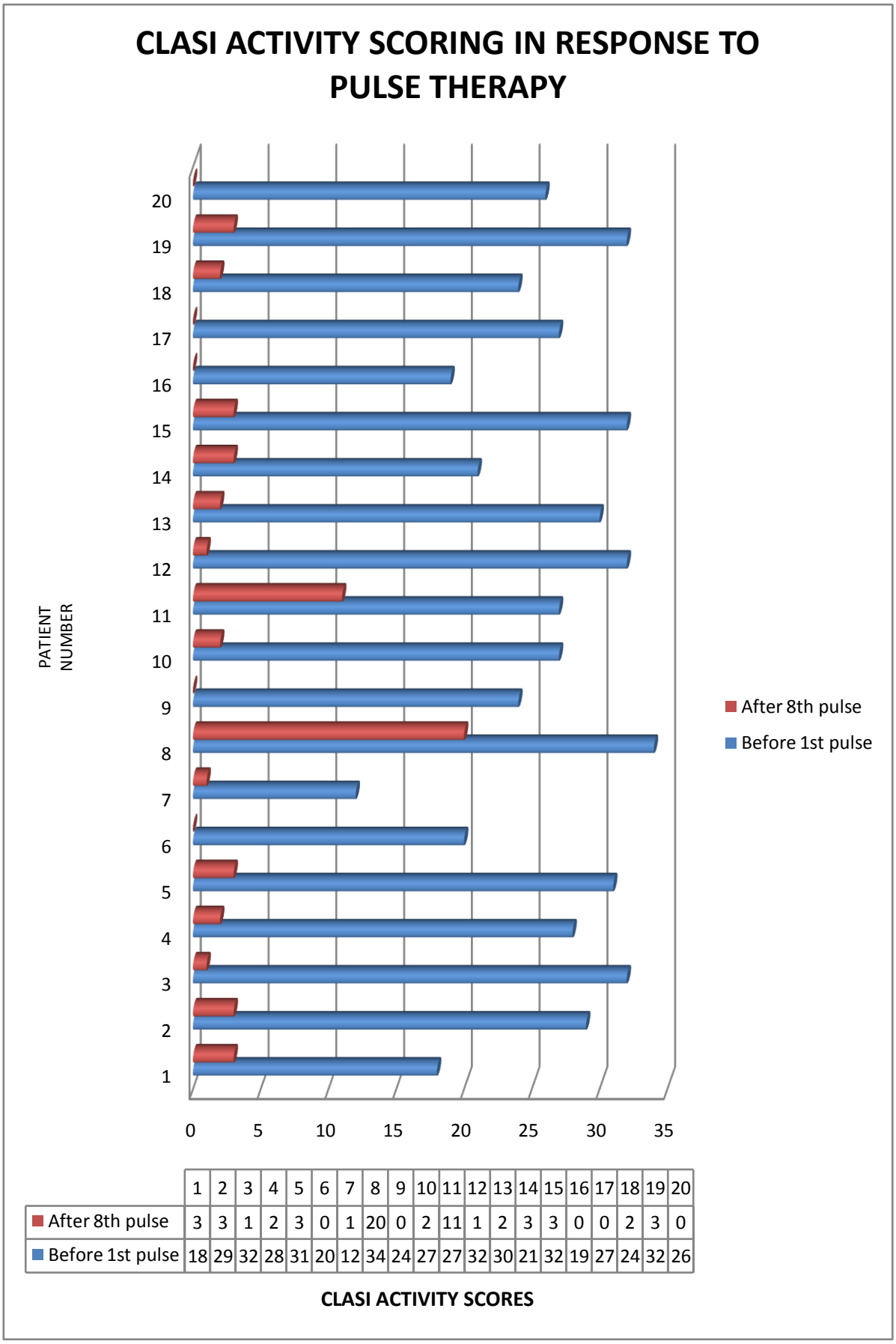
The overall cutaneous response in each patient as quantified by the Cutaneous Lupus Area and Severity Index (CLASI) is as shown in the figure 3.

PHOTOSENSITIVITY:

A history of photosensitivity was noted in all but on patient which is 95% of the study population. At the end of 8 cycles of pulse therapy, photosensitivity disappeared in all but 3 patients (15%)

MALAR RASH:

The characteristic malar rash was present in 17 out of the 20 patients (85%).At the end of 8 pulses, there was complete disappearance of malar rash in 14 patients with percentage improvement of 82%.



	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
After 8th pulse	3	3	1	2	3	0	1	20	0	2	11	1	2	3	3	0	0	2	3	0
Before 1st pulse	18	29	32	28	31	20	12	34	24	27	27	32	30	21	32	19	27	24	32	26

DISCOID RASH:

Discoid rash was the most common manifestation presenting in 100% of the patients at the start of pulse therapy. At the end of 8 pulses,7 patients (35%) had complete disappearance of the discoid rash. In the rest of the patients there was moderate improvement with lesions showing minimal scaling in 11 patients (55%). There was a persistence of discoid rash in only 2 patients (10%).

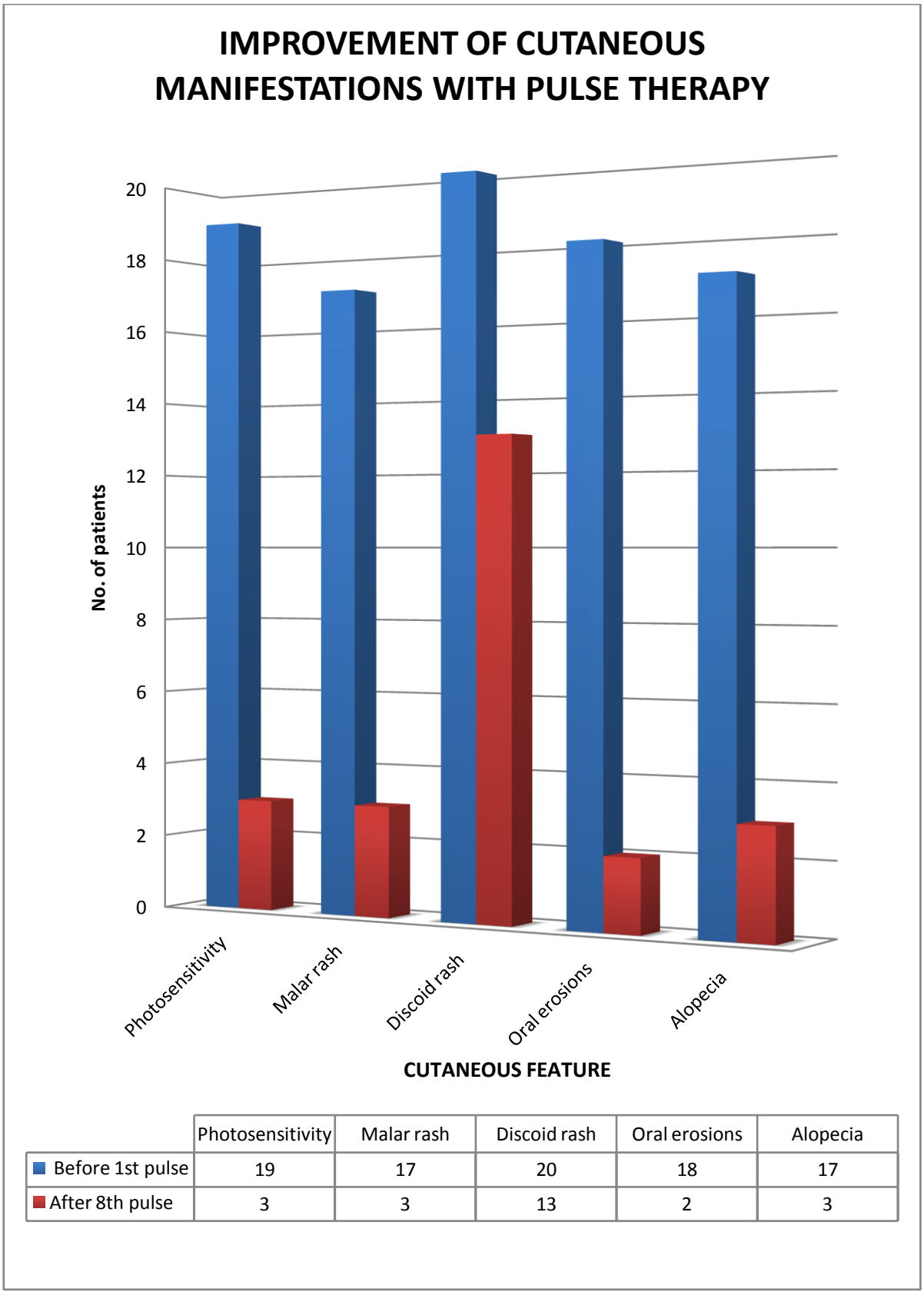
ORAL EROSIONS:

At the initiation of the study, oral erosions were present in 18 out of the 20 patients (90%). At the end of 8 cycles of pulse therapy there were persistent erosions only in 2 patients with percentage improvement of 88%.

ALOPECIA:

Alopecia was seen in 17 out of the 20 patients (85%). There was diffuse alopecia in all 17 patients, whereas lupus hair was seen in 6 patients. At the end of 8 cycles of pulse therapy, clinically appreciated alopecia was seen in 3 patients. Alopecia improved in 14 patients with a percentage improvement of 82%.

The overall improvement of individual cutaneous feature with pulse therapy is represented graphically in figure 4.



	Photosensitivity	Malar rash	Discoid rash	Oral erosions	Alopecia
Before 1st pulse	19	17	20	18	17
After 8th pulse	3	3	13	2	3

Figure 3

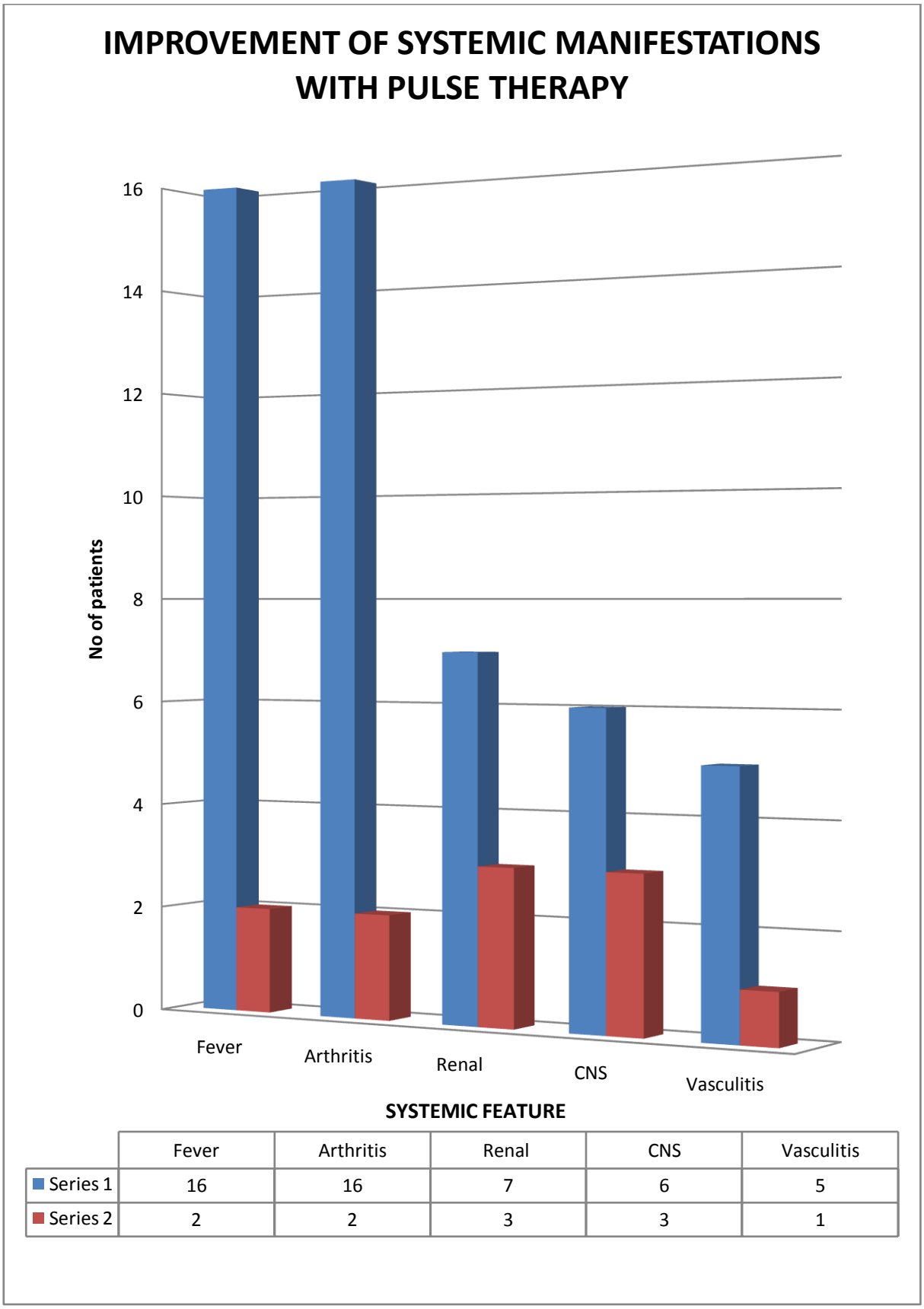
FEVER:

At the initiation of pulse therapy, fever in the absence of any focus of sepsis was recorded in all but 4 patients who comprise 80% of our study population. Fever in most cases was of low grade and intermittent in nature. With the completion of 8 pulses, fever was noted in 2 patients (10%). Both the patients initially became afebrile soon after the first pulse, but it reappeared after the 6th pulse in one patient and after the 7th pulse in another.

SYSTEMIC MANIFESTATIONS:

All but 3 patients had systemic manifestations before the initiation which amounted to 85% of the study population. The most common systemic manifestation was joint involvement with non erosive arthritis being reported in 80% (16 patients), followed by renal involvement in 35% (7 patients). 6 patients (30%) had neurological involvement, of which 5 of them had seizures whereas one patient had altered behaviour and she went on to develop seizures after the pulse. There was vasculitis in 5 of the patients(25%) of which 2 patients (10%) had retinal vasculitis and presented with diminished vision. The rest 3 patients had vasculitic ulcers. There was serositis in one patient (5%). Similarly, pulmonary involvement with interstitial pneumonitis was reported in one patient (5%) before the start of pulse therapy.

At the end of 8 cycles of pulse therapy, 5 patients (25%) continued to have systemic manifestations. Feverand arthralgia were present in 2(10%), renal and CNS involvement in 3 patients and vasculitis in 1 patient. One patient newly developed interstitial lung disease after 7 pulses.



	Fever	Arthritis	Renal	CNS	Vasculitis
Series 1	16	16	7	6	5
Series 2	2	2	3	3	1

Figure 4

ANTI dsDNA LEVELS:

All the patients except one (95%) showed positivity for anti dsDNA as measured by the immunofluorescence technique. The anti dsDNA values were quantified in serial dilutions. It was of low titres up to 1 in 40 in six patients (30%). In four patients (20%) there was a very high titre positivity of 1 in 1280. The other nine patients (45%) had moderate titres ranging from 1 in 160 to 1 in 640.

After 8 cycles of pulse therapy there was a fall in titres in all patients excluding two (10%) whose titres remained at very high levels of 1 in 1280 dilutions. Anti dsDNA antibody became negative in 6 patients (30%). The fall in titres was by 2 to 4 folds in most other patients. Of these, 10 patients (50%) had low titres of upto 1 in 40 dilutions. 3patients (15%) continued to have moderate values.

Overall, 2 patients (10%) had a static titre of anti dsDNA antibodies. The rest (90%) showed a fall in titre. No patient showed increase in anti dsDNA antibody titres.

The anti dsDNA levels before and after 8 pulses was statistically analysed using the paired‘t’test.

The mean of variance was 319; the standard error of the difference was 92.516. The final t value was 3.45. The p value for the given t values and degree of freedom was less than 0.005, hence the difference between the 2 groups was statistically significant.

Hence there was a statistically significant fall in the anti dsDNA levels after 8 pulses.

ANTINUCLEAR ANTIBODIES (ANA):

The anti nuclear antibody showed very high levels 1:1280 in 2 patients, high levels (> 1: 160) in 7 , moderate levels (1: 80) in 2 patients and low levels (1:40 & 1:10) in 10 patients. So at the start of pulse therapy 50% of patients had low levels, 10% of patients had moderate levels, high levels in 35% and very high levels in 10%.

After 8 pulses ANA was negative in 4 patients (20%), low levels in 14 patients (60%), and moderate levels in 2 patients (10%).

The most common pattern observed was rim or peripheral pattern in 9 patients (45%) followed by homogenous pattern in 8 patients (40%) and speckled pattern in 3 patients (15%).

There was no absolute correlation between the disease activity and antinuclear antibody levels. Also the pattern of ANA did not influence the response to pulse therapy.

ERYTHROCYTE SEDIMENTATION RATE:

At the initiation of pulse therapy ESR was elevated in 15 patients (75%). At the end of 8 pulses it remained elevated in 5 patients. The percentage improvement was 66%. The ESR values had good correlation with systemic disease activity than cutaneous disease activity.

TOTAL LEUCOCYTE COUNT:

There was no significant decrease in total leukocyte count in any of the patients at the initiation of pulse therapy. There was no correlation with disease activity and total leukocyte count.

DURATION TAKEN FOR CLINICAL REMISSION:

All the cutaneous features showed improvement with pulse therapy, showing improvement beginning from the first pulse itself. Photosensitivity started showing improvement after a minimum of 3 pulses. The average duration taken was around 5 months in 85% of the patients.

Malar rash took a minimum of 2 pulses up to 5 pulses to disappear in 15% it still persisted at the end of 8 pulses. The average time duration taken for improvement of malar rash was 3.5 months. Among the cutaneous lesions, oral lesions were the first to show improvement. It took a minimum of 1 and a maximum of 3 pulses for improvement. The average duration required was 2.3 pulses in 90% of the patients. Discoid rash showed improvement only by 8^{th} pulse with persistence of minimal scaling of discoid rash over the concha in almost all patients. Alopecia started to improve after the minimum of 3 pulses. The time duration noted here is the duration taken for the beginning of regrowth. The average number of pulses required was 5 in 70 % of the patients.

Among the systemic manifestations, fever improved in all the patients after the first pulse. But in 2 patients it reappeared after the 6^{th} and 7^{th} pulses respectively. The arthralgia required a minimum of two to a maximum of 6 pulses to disappear in 87% of the patients who had non erosive arthritis at the beginning of treatment.

The duration taken for clinical remission of the cutaneous and systemic manifestations in each patient is represented in Figure 5.

ADVERSE EFFECTS:

The overall incidence of adverse effects was low. The commonest side effect noted was menstrual irregularities in 4 patients. There was oral candidiasis in 5 patients. Pyogenic skin infections were noted in 2 patients. Urinary tract infections were observed in 3 patients. One patient developed acneiform eruptions after the 3^{rd} pulse. There was a fall in platelet count in 2 patients, following which pulse therapy was withheld for 2 weeks and continued after the values normalised. None of the patients required platelet transfusions. There was darkening of complexion reported in 1 patient.

Figure 5

DURATION TAKEN FOR CLINICAL REMISSION

Patient No	Photosen -sitivity	Malar rash	Discoid rash	Oral erosions	Alopecia	Fever	Joint pain
1	4	4	8+	3	4	1	3
2	5	3	8+	2	-	1	4
3	5	4	8+	3	5	1	2
4	6	4	8+	2	6	1	1
5	6	3	8+	2	7	1	6
6	4	4	6	-	6	1	-
7	5	4	8+	2	6	-	-
8	8+	8+	8+	4++	8+	6++	8+
9	3	2	6	1	4	1	6
10	6	4	8+	2	3	1	5
11	8+	8+	8+	6++	8+	7++	7++
12	4	4	8+	3	7	1	4
13	6	5	8+	2	3	1	5
14	8+	8+	8+	-	6	1	6
15	6	3	8+	1	6	1	-
16	-	-	6	2	6	1	-
17	7	4	7	1	4	1	4
18	5	5	8+	2	-	-	7
19	6	4	8+	3	6	1	4
20	6	4	6	2	3	1	3

+: Persistence of activity.

++: Relapse of activity.

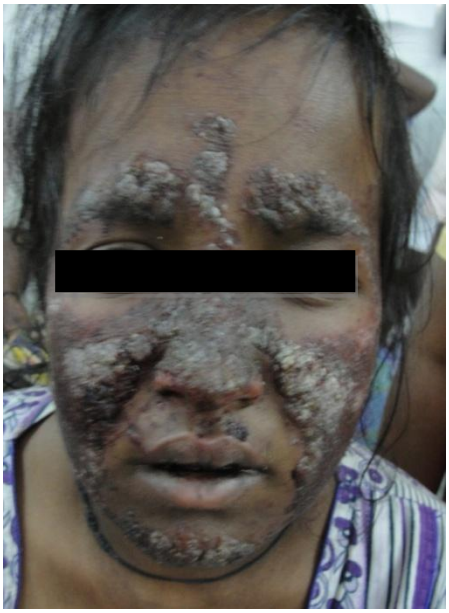
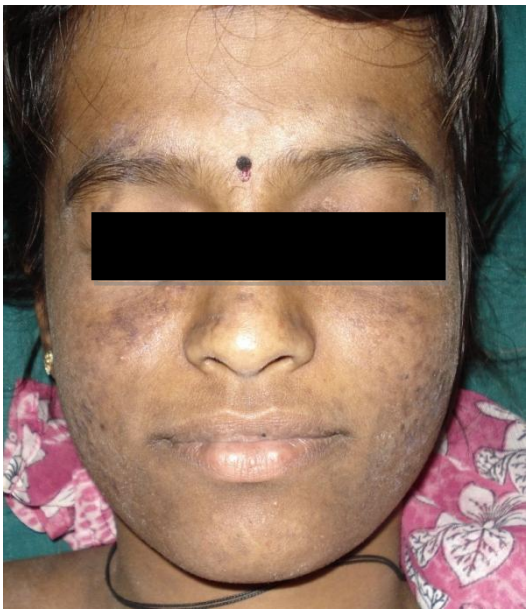
DURATION OF PULSE THERAPY REQUIRED:

Among the 20 patients, 7 patients (patient no.3, 7, 9, 12, 16, 17, 20) who had a CLASI score of 0-2 with no systemic manifestations at the end of 8 cycles were taken off the first phase and moved into second phase. 6 patients who had a CLASI score of 3-10 and also had slightly elevated anti dsDNA titres were given a total of 10 pulses in the phase I and then moved on to phase II. Patient no. 1 who had pulmonary disease and patient no.6 who still had neurological involvement and a high titre of anti dsDNA of 1 in 160 required an additional of 6 more pulses in phase I. Patient no.11 received total of 18 pulses in phase I.

In the eighteen patients who have completed phase I so far, the mean number of pulses required in phase I was 9.

Patient no.18 is still in Phase I at 11 pulses. Patient no. 8 defaulted after the 9^{th} pulse. None of the patients in phase II showed relapse of disease activity so far.

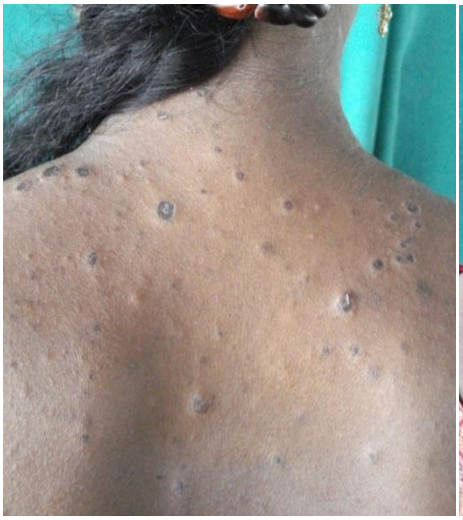
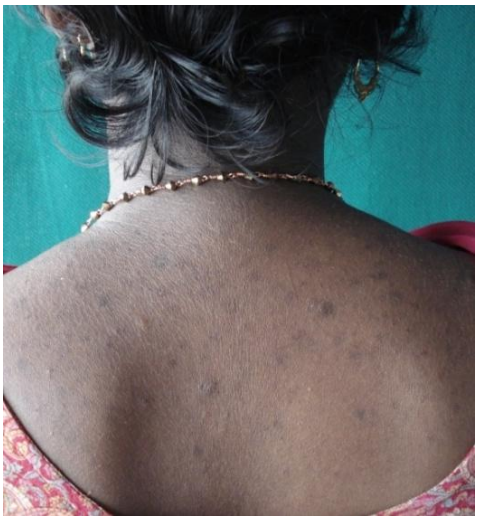
MALAR RASH

Before first pulse

After eighth pulse

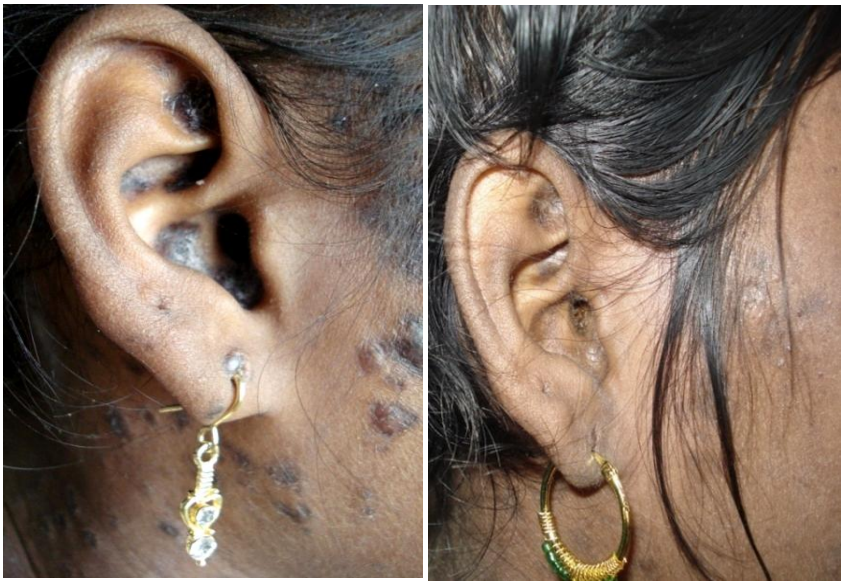
DISCOID RASH

Before first pulse

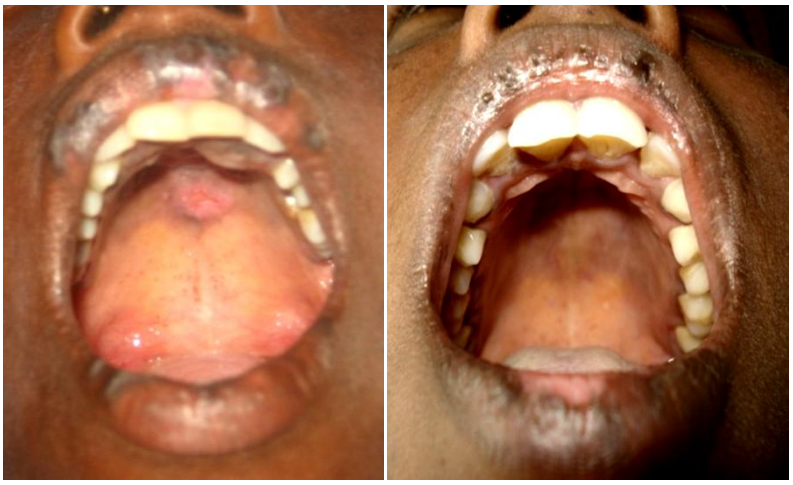
After eighth pulse

SCHUSTER'S SIGN



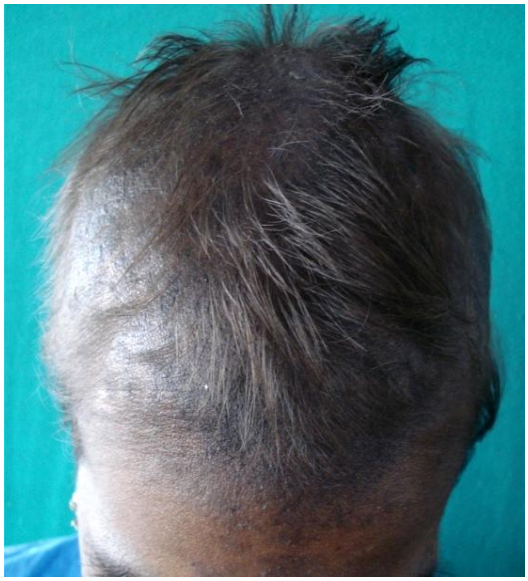
Before first pulse After eighth pulse

ORAL EROSION

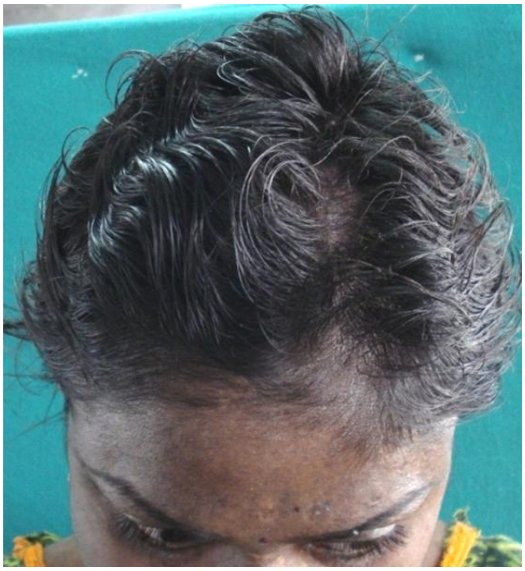


Before first pulse After eighth pulse

ALOPECIA – LUPUS HAIR



Before first pulse



After eighth pulse

RESULTS OF DEXAMETHASONE CYCLOPHOSPHAMIDE PULSE THERAPY IN SCLERODERMA:

16 patients of Systemic Sclerosis diagnosed as per the ARA criteria were given dexamethasone cyclophosphamide pulse therapy. All the patients were evaluated at the end of 12 pulses.

AGE: The age distribution of patients with scleroderma included in the study varied from a minimum of 17 years to amaximum of 54 years. The highest number of patients were in the age group of 31-40 years (5 patients, 31%), followed by 25% (4 patients) each in the age group of 21-30 and 41-50. There were only 2 patients 12.5% above 50 years of age and one patient less than 20 ears of age. Literature reports a peak age of onset between 30-50 years which is the child bearing age and declines after menopause.

SEX DISTRIBUTION: The male to female ratio was 16:1. This is similar to the figures in literature which range from 5:1 to 14:1.

DURATION OF ILLNESS: The duration of illness ranged from a minimum of 1 year to a maximum of 10 years. The average duration of illness was 3.4 years before the start of pulse therapy.

TYPE OF DISEASE: Among the 16 patients, 62.5% (10 patients) had diffuse cutaneous systemic sclerosis and 37.5% (6 patients) had limited cutaneous systemic sclerosis.

RAYNAUD'S PHENOMENON:81.25% (13 patients) gave a history of Raynaud's phenomenon at the beginning of pulse therapy. Following pulse therapy, no more episodes of Raynaud's was reported inall the patients. The average duration taken for resolution averaged around 4 pulses.

DIGITAL ULCERATION/SCARRING: 87.5% (14 patients) had digital pitted scars at the start of treatment. After 12 pulses there was absence of development of new scars in all (100%) patients though the scars showed only a mild improvement in 6 patients.

PIGMENTARY CHANGES: Salt and pepper pigmentation ranging from minimal to marked was observed in all patients prior to pulse therapy. A complete disappearance of salt and pepper pigmentation was noted in all but one patient.

FURST ET AL SKIN SCORING:

The distribution of the degree of skin sclerosis as measured by the Furst et al scoring is as follows:

FURST SKIN SCORE	BEFORE FIRST PULSE	AFTER THE 12TH PULSE
Severe (21-30)	2	1
Moderate (11-20)	10	6
Mild (1-10)	4	9

From the table it is evident that initially there were more number of patients with moderate degree of skin sclerosis, After 12 pulses the severity of sclerosis has decreased resulting in more number of patients with mild degree of sclerosis. Of the 16 patients all but one continued to have severe sclerosis. The percentage improvement was 93.7%.

The degree of improvement in the individual skin scores was studied using the paired‘t’ test,

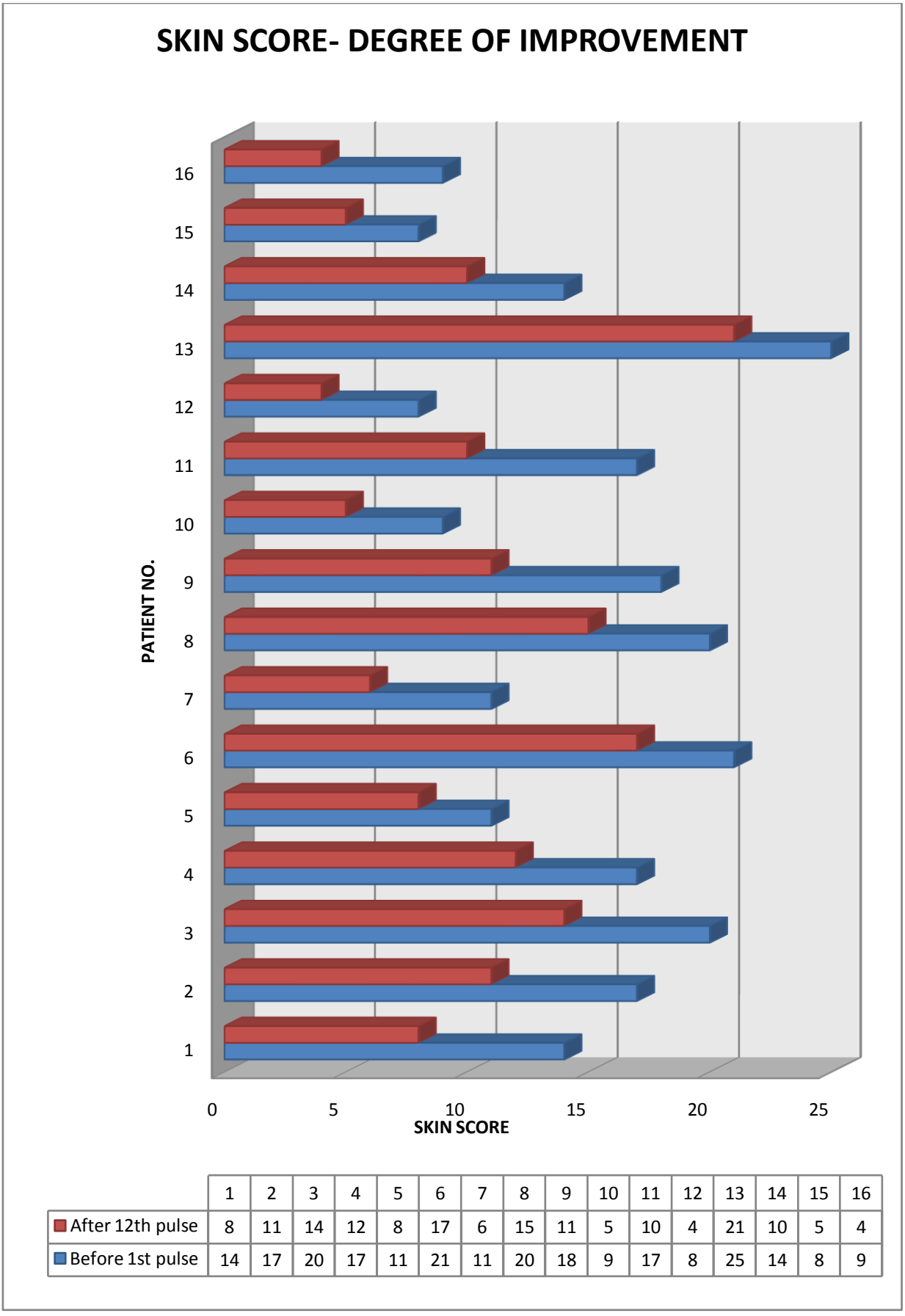
Where, thestandard error of difference = 0.319

t = 15.0816.

The two-tailed P value is less than 0.0001

By conventional criteria, this difference is considered to be extremely statistically significant.

The degree of improved in the individual skin scores is represented in the following figure 6.



	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
After 12th pulse	8	11	14	12	8	17	6	15	11	5	10	4	21	10	5	4
Before 1st pulse	14	17	20	17	11	21	11	20	18	9	17	8	25	14	8	9

Figure 6

DYSPHAGIA:

At the beginning of pulse therapy 10 (62.5%) patients had dysphagia ranging from mild to severe degree. There was mild to moderate degree of improvement in dysphagia with 12 pulses. At the end of 12 pulses, 5 patients (32.5%) continued to have dysphagia. The percentage improvement is 50%. In one patient with severe dysphagia, endoscopy guided oesophageal dilatation was done following which there was marked improvement in dysphagia.

PULMONARY FUNCTION TESTS:

Of the 16 patients all 10 patients with diffuse systemic sclerosis had pulmonary involvement in the form of interstitial lung disease. The degree of restrictive lung disease was graded according to FVC levels as mild (<30), moderate (30-50) and severe (>50). The distribution of pulmonary disease before and after treatment is as follows:

Grade of restrictive lung disease	Before first pulse (No of patients)	After12th pulse (No of patients)
Nil	6	11
Mild	4	2
Moderate	5	2
Severe	1	0

Only those who had nil disease were considered to have significantly improved. The percentage improvement was 60%

OTHERS:

One patient had myositis with features of proximal muscle weakness with an initial creatine kinase level (CPK-MB) of 2828U/L. After 6 pulses there was complete absence of muscle pain and the muscle power showed complete recovery. The creatine kinase level was normal at 192U/L.

2 patients had renal involvement with elevation of 24 hour urine protein, and mild elevation of serum creatinine. The renal functions normalised after 3 pulses in one patient and after 2 pulses in another. The blood pressure remained normal in both patients.

There was no cardiac involvement or calcinosis cutis in any of the patients.

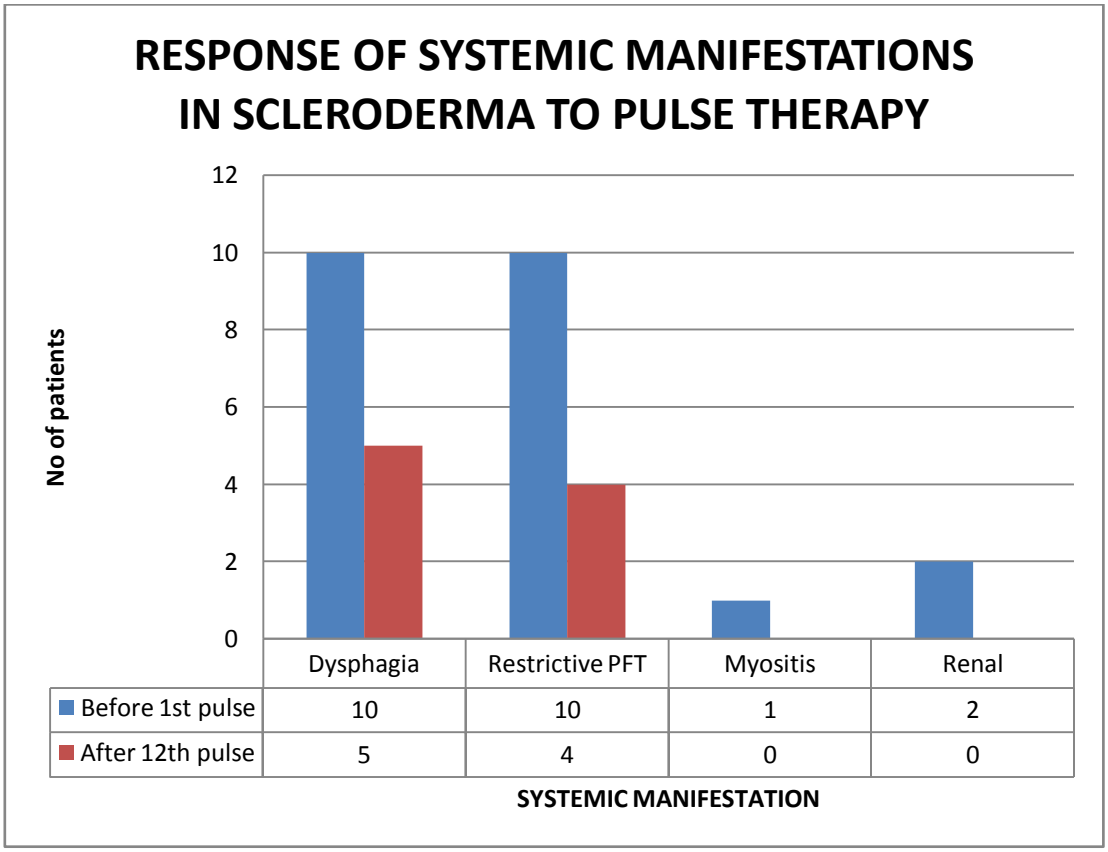


Figure 7

ERYTHROCYTE SEDIMENTATION RATE (ESR):

ESR was elevated in 11 out of the 16 patients (68%) of the patients. At the end of 12 pulses the ESR was within normal limits in all patients.

ANTI NUCLEAR ANTIBODY:

ANA was positive in 4 out of the sixteen patients at titres of 1 in 40. It was of speckled pattern in all four.

ADVERSE EFFECTS:

Minor adverse effects were noted in 7 patients. 1 patient reported weight gain and also had menstrual irregularities. Frequent upper respiratory tract infections were noted in 4 patients. Recurrent urinary tract infection was noted in 1 patient. Herpes zoster occurred in 1 patient. In one patient who had an initial mantoux positivity,pulse therapy was given under cover of ATT and no complications were noted.

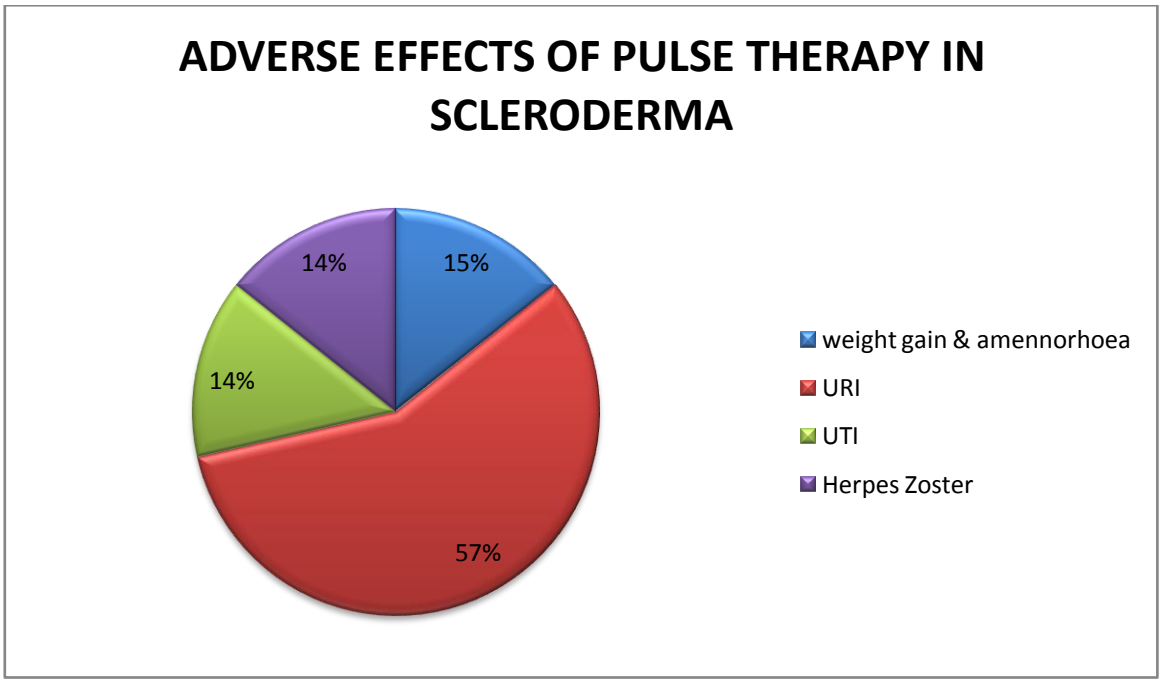
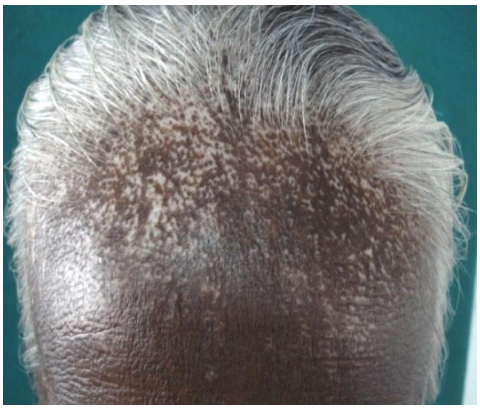
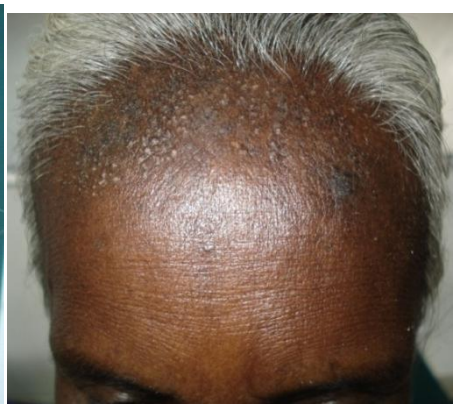

ADVERSE EFFECTS OF PULSE THERAPY IN SCLERODERMA
15%
57%
14%
14%
weight gain & amennorhoea
URI
UTI
Herpes Zoster

Figure 8

SALT AND PEPPER PIGMENTATION

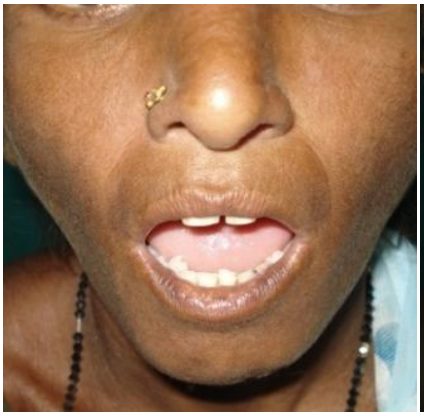


Before first pulse

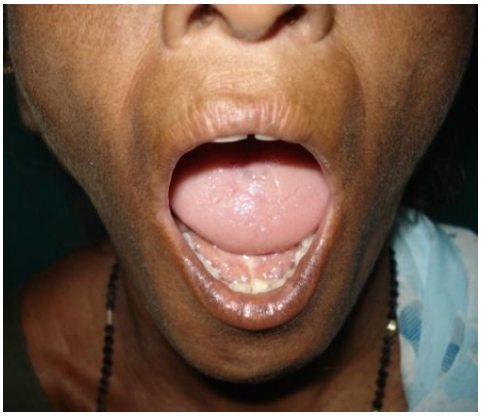


after 12th Pulse

MOUTH OPENING

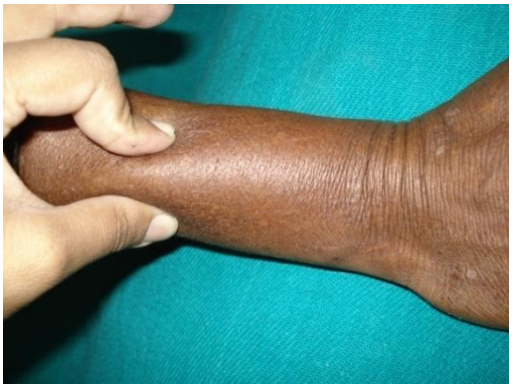


Before 1st Pulse

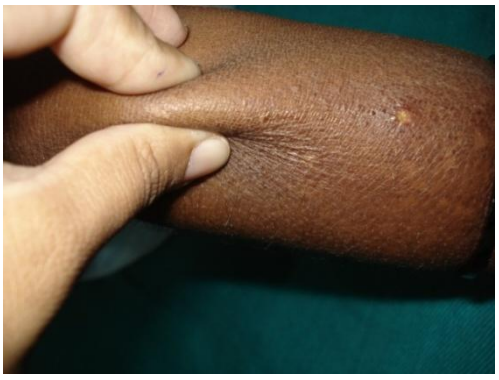


After 12th Pulse

SCLEROSIS OF SKIN



Before 1st pulse



After 12th Pulse

DISCUSSION

SYSTEMIC LUPUS ERYTHEMATOSUS:

Though there has been widespread use of pulse therapy for systemic lupus erythematosus in a number of centres especially in India, there a only a few previous studies which have a detailed measure of the efficacy of dexamethasone cyclophosphamide pulse therapy in the treatment of systemic lupus erythematosus.

The mean age of our patients was much less than the average age reported in literature. Also, there were a more number of female patients reported than in other studies.

The most common skin manifestation in our study was discoidrash (100%) whereas in other studies it occurred in a frequency ranging from 25-50 %. This discrepancy may be due to the study being conducted in the department of dermatology and only those patients with skin manifestations were included in the study.The most common manifestation in other studies was photosensitivity, which was the second most common (90%) in our study, along with oral erosions. Malar rash and hair loss was noted in 85% each were in other studies it ranged from 70-75%. Among the systemic manifestations arthritis was reported in 80% of our patients whereas in other studies it was around 57% in Indian studies to 90% reported in western literature. Renal involvement was seen in 35% in our study in concordance with other studies where it was between 21.4%-67%.

- The cutaneous feature to show an early response was oral erosions which resolved after a mean of 2.3 pulses in our study. A similar figure of 1-3 pulses has been reported by Dhabhaiet al[5] and Pasricha et al[47]. The percentage improvement was 88%
- Malar rash took an average of 3.5 pulses for resolution, similar to that observed by Dhabhai et al[5] (2-5 pulses)
- Discoid rash took a longer duration, the earliest being 6 pulses for resolution. In 75 % of our patients it was still persistent with minimal scaling without any erythema at the end of 8 pulses. Previous studies also indicate that discoid rash was difficult to treat taking anywhere between a minimum of 2 pulses to a maximum of 16 pulses for complete resolution.
- Alopecia responded after 2-7 pulses at a mean of 5 pulses. Statistics by Dhabhaiet al[5] also report similar figures of 2-6 pulses for resolution, with the longest duration required being 17 pulses in one case.
- Similar to previous study published by Dhabhaiet al[5] and Sudip et al[48], fever was the earliest to respond. In most cases it resolved with one pulse, which was same as the duration observed in other studies. The percentage improvement in our study with one pulse was 90% which is similar to that seen by Sudip Das et al[48].
- The number of pulses taken for remission of arthritis showed a wide variation, responding after the very first pulse in one patient whereas in some it took upto 6 pulses. The mean duration in most cases was 4.2 pulses. In the Dhabhai ET al[5] study, the mean duration was also a similar 4 pulses. The range was from 2-11 pulses.

- Of the 7 patients who showed renal involvement in our study, there was an initial favourable response in all of them with renal parameters and 24 hour urine protein normalising after 1-3 pulses. Out of these at least 3 patients showed exacerbation of renal disease. In the previous study, nephritis was reported only in fewer patients (4) with persistence of nephritis in 75% even after 12 pulses.
- The seizures showed a remission after 5 pulses in this study whereas remission was reported after 8 pulses by Dhabhai ET al[5].
- The anti dsDNA antibodies became negative in 35% of patients after the 8 pulses which was similar to the figures reported by Dhabhai et al where 33% showed negative anti dsDNA after 8 pulses. The exact number of pulses required for the anti dsDNA levels to become negative in each patient could not be calculated in this study, since the measurements were taken at long intervals- i.e. at the initiation of pulse therapy, after 8 pulses and after 12th pulse in those who continued to have disease activity. In the previous studies the minimum duration to achieve a negative anti dsDNA level was 4 pulses.
- In a nutshell, though subjective improvement was reported beginning with the first pulse itself, objective improvement of most of the cutaneous manifestations were seen commonly around the fourth pulse. The serological parameters improved by 8 pulses in the majority of the patients.
- The overall adverse effect profile observed in this study was low. Common side effects of pyogenic skin infections and candidiasis were similar to that noted in previous studies. Generalised pigmentation of skin was reported in one patient which was also observed by Dhabhai et al and Pasricha et al[4].

Acneiformeruptions were seen in one patient in our study which was not reported in the previous studies Pasrisha et al have reported generalised pruritus which was not seen in our study. Menstrual irregularities were seen in 35% of our patients. Previous studies have not mentioned any reports of menstrual irregularities.

- Dhabhaiet al[5] have reported cardiac arrest proving fatal in one patient. No such adverse effects were noted in any of our patients.

SYSTEMIC SCLEROSIS:

- In our study the age of majority of the patients was between 25-45 years in accordance with figures reported in earlier studies. Interestingly in our study two patients reported after menopause at 51 and 54 years of age.
- The female to male ratio was 16:1. This is similar to the figures in literature which range from 5:1 to 14:1.Indian study by Viswanathet al[49] gives a similar figure of 13:1.
- The skin score showed a good correlation with disease activity similar to that observed in previous studies. The response of skin scores to pulse therapy was also statistically significant. Similarly Ahmed et al[6] reported moderate to marked improvement in skin scores with pulse therapy.
- Viswanathet al[49] reported that no new digital ulcers developed after the patients were started on pulse therapy although the existing scars showed only a mild improvement. This finding was confirmed in our study.
- Raynaud's phenomenon was noted in 82.5% of our patients while it was noted in 100% of the patients by Ahmed et al[6] and Sudip et al[48]. This difference is

probably due to the warmer climatic conditions in our part of the country compared to the Ahmed et al[6] study which was conducted in Kashmir. Similarly, the response of Raynaud's phenomenon to pulse therapy was much higher in our study (100%) compared to the Ahmed et al study which reports a marked improvement in 69% of the patients

- Dysphagia was reported in 62.5% of our patients compared to the 30% observed by Ahmed et al[6]. The response of dysphagia to pulse therapy was only of a moderate degree similar to that observed by Ahmed et al[6]. Sudipet al[48] mention a percentage improvement of 38.5% of dysphagia. The percentage improvement in our study is 62.5%. In one of our patients who had severe dysphagia, endoscopy guided surgical dilatation had to be resorted to.
- Pulmonary function tests showed a marked improvement in 60% of our patients. The improvement was observed beginning from the 3rd month with significant improvement after 6 pulses. Ahmed et al[6] have shown improvement in breathlessness in 50% although they did not employ pulmonary function tests for assessment and only improvement of breathlessness was recorded. Sudipet al[48] give a percentage improvement of 61.5% for breathlessness.
- Though subjective improvement was reported by the patients at 3-4 pulses, objective improvement of skin sclerosis was observed only after 6-8 pulses. The laboratory measures of PFT showed significant improvement in the majority after 6 pulses
- The average duration of pulse therapy given was 12-18 pulses in the study conducted by Ahmed et al[6]. In our study the minimum number of pulses was 12.

- In our study we noted a marked improvement in the salt and pepper pigmentary changes. The previous studies do not give ay detailed account of the response of pigmentary changes except for one case report by Pasrisha et al who reported complete reversal of pigmentary changes.
- Weight gain was noted in one patient in our study. Here it was also associated with amenorrhoea. It was not reported in the study by Ahmed et al[6]. Tuberculous cervical lymphadenopathy was reported by Ahmed et al., but no such reactivation of Tuberculosis was noted in any of our patients. We noted increased incidence of minor upper respiratory tract infections which was also reported by Ahmed et al and Pasrichaet al[47].
- Studies by Davaset al[50], have reported haemorrhagic cystitis in isolated cases when cyclophosphamide pulse was used in the treatment of lung disease in scleroderma. Similar complication was observed by C R Srinivaset al.[52], who suggested that cyclophosphamide I V should be given on the second day of pulse along with pre and post hydration.Meticulate instructions to the patient in maintaining hydration and frequent voiding of the bladder prevent this dreaded complication.
- Though there have been differences of opinion regarding the precipitation of scleroderma renal crises by high dose corticosteroids, we did not observe any such complication in any of our patients even in those 2 patients who had renal involvement. This is similar to the view observed by Pasrisha et al and Ramam et al[22].Careful selection of patients and monitoring and appropriate treatment of blood pressure will help in avoiding scleroderma renal crisis

- Kanwar AJ et al[44] reported hiccups as a specific side effect of pulse therapy. Interestingly none of our patients treated for SLE or Scleroderma developed this side effect.

CONCLUSION

The following are theconclusions derived from this study

- Dexamethasone cyclophosphamide pulse therapy is an effective therapeutic option for treatment of SLE and Scleroderma.
- Rapid induction of and prolonged remission is achieved with pulse therapy.
- Pulse therapy is safer than oral steroids with respect to decreased HPA axis suppression and decreased osteopenia.
- Patient compliance is much better with pulse therapy because of the rapid induction of remission and relative absence of side effects.
- Though the duration of phase I of pulse therapy is arbitrary depending upon the degree of remission achieved in individual patients, the mean duration required would be 9 pulses in SLE while in Scleroderma, a longer phase I of up to 12-15 months is required.
- Unlike in bullous disorders where clinical signs of activity are clear, it is not so in collagen vascular disease. Hence an extended phase I and phase II should be given to attain remission.
- The earlier the initiation of pulse therapy in scleroderma the better is the response.
- Precipitation of scleroderma renal crisis was not observed in any of our patients and hence high dose corticosteroid pulse is safe in scleroderma provided blood pressure is maintained within normal limits by anti hypertensives.

- Scope for future improvements in pulse therapy for collagen vascular disease is ample with respect to clear guidelines on the duration of therapy and the necessity of daily cyclophosphamide

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ANNEXURES

PROFORMA

Name

Age

Sex

Socio economic status

Complaints

SLE:

- Skin lesions.
- Oral ulcers
- Photosensitivity
- Arthralgia
- Fever
- Pleurisy
- Seizures
- Psychiatric symptoms

SYSTEMIC SCLEROSIS:

- Tightness of skin
- Swelling of hands & feet
- Pigmentary changes
- Raynaud's phenomenon

- Finger tip ulcers
- Difficulty in mouth opening
- Dysphagia
- Abdominal pain & alteration in bowel habits
- Tightness of chest, difficulty in breathing.

History to rule out active infections

History of hypertension, diabetes mellitus, ischaemic heart disease.

Duration of illness

Clinical features:

SLE:

- Malar rash
- Discoid rash
- Oral ulcers
- Alopecia
- Joint swelling & joint line tenderness
- Anaemia
- Fever
- Systemic examination of CVS, RS, GIT & CNS

SYSTEMIC SCLEROSIS

- Sclerosis of skin
- Edema of hands & feet

- Digital ulcers& stellate scars
- Pigmentary changes
- Cyanosis
- RS: Reduced chest expansion.
- CVS
- Per Abdomen

Diagnosis

Investigations

Diagnostic tests

Complete haemogram

ANA

Anti – ds DNA

VDRL

Skin biopsy

Tests to rule out systemic involvement:

Renal: Blood urea, serum creatinine, urine routine & 24 hour urinary protein.

Cardiac: ECG, Echocardiograph

Pulmonary:X ray chest, pulmonary function tests.

G.I: Barium swallow, OGD scopy.

Tests to rule out latent tuberculosis: Mantoux

Tests before every pulse: Complete haemogram, blood sugar, renal function tests, serum electrolytes, urine routine.

Tests after every pulse: serum electrolytes & urine for RBCs.

ANA titre repeated every 4 months.

Anti – ds DNA after 8 pulses

CONSENT FORM

I _____, give my free and full consent to Dr._____ for the purpose of undergoing pulse intravenous injections for my illness, the nature and consequences of which have been explained to me. I have been completely explained the procedure, the need for repeated investigations, its results and possible side effects. I understand that more than one session may be needed for obtaining results. I understand the limitations of the procedure and also the final results. I have been provided adequate opportunity to seek information or withdraw from the study anytime during the study.

_____

Signature of the patient/ guardian.

_____

Signature of doctor.

_____-

Signature of witness.

SCLERODERMA MASTER CHART

Patient No	Name	Age	Sex	Duration (years)	Type of disease	Skin Score		Raynauds		Digital ulcer /scars		Salt and pepper pigmentation		PFT- Degree of restrictive lung disease		G.I.T		Others	ESR		ADR
						B	A	B	A	B	A	B	A	B	A	B	A		B	A	
1	Manimegalai	29	F	2	D	14	8	-		+		+	-	Mild	N	+	-	Myositis	7/14	6/14	Wt gain
2	Sarawathy	54	F	3	D	17	11	+		-		++	-	Mild	N	-	-	Renal	22/45	7/13	URI
3	Thangakani	38	F	6	D	20	14	+	-	+		+	-	Moderate	N	++	+	-	31/45	6/12	
4	Nirmala	41	F	5	D	17	12	+		+		++	-	Moderate	Mild	++	+		27/52	5/11	URI
5	Selvi	35	F	3	L	11	8	-		+		+	-	Normal	N	-	-	-	9/14	7/13	
6	Rahima	31	F	5	D	21	17	+		+		++	-	Moderate	Mild	++	+	-	35/51	8/15	URI
7	Kala	37	F	4	L	11	6	+		+		+	-	N	N	+	-	-	9/16	5/13	
8	Pushpavalli	42	F	7	D	20	15	+		+		+	-	Severe	Moderate	+++	S	-	32/68	6/11	Reactivation of TB
9	Anitha	30	F	6	D	18	11	+		+		+	-	Moderate	N	+	-	-	24/53	7/13	URI
10	Mala	44	F	3.5	L	9	5	-		-		+	-	Nil	N	-	-	-	18/34	4/11	
11	Fathima	52	F	1	D	17	10	+		+		-	-	Mild	N	+	-		27/49	5/13	
12	Krishnaveni	27	F	2	L	8	4	+		+		-	-	Nil	N	-	-	-	20/45	6/13	
13	Shekar	49	M	10	D	25	21	+		+		++	+	Moderate	Moderate	+++	++	Renal	34/70	7/16	
14	Poongodi	17	F	2	D	14	10	+		+		+	-	Mild	Normal	+	-	-	22/58	6/11	
15	Lakshmi	34	F	1.5	L	8	5	+		+		-	-	Nil	N	-	-	-	7/13	7/11	
16	Maheshwari	26	F	2	L	9	4	+		+		+	-	Nil	N	-	-	-	19/34	8/15	UTI

SYSTEMIC LUPUS ERYTHEMATOSUS- MASTER CHART

Pt.No	NAME	AGE	SEX	Duration - months	CLASI		Photo sensitivity			Malar rash			Discoid rash			Oral erosions			Alopecia			FEVER		
					Before	After	B	A	D	B	A	D	B	A	D	B	A	D	B	A	D	B	A	D
1	Ponni	29	F	24	18	3	+	-	4	-	-	4	+	+	8+	+	-	3	+	+	4	+	-	1
2	Krishnamurthi	24	M	18	29	3	+	-	5	-	-	3	+	+	8+	+	-	2	-	-	-	+	-	1
3	Rekha	17	F	6	32	1	+	-	5	+	-	4	+	+	8+	+	-	3	+	-	5	+	-	1
4	Lakshmi	19	F	2	28	2	+	-	6	+	-	4	+	+	8+	+	-	2	+	-	6	+	-	1
5	Lalitha	28	F	12	31	3	+	-	6	+	-	3	+	-	8+	+	-	2	+	-	7	+	-	1
6	Soundari	27	F	4	20	0	+	-	4	+	-	4	+	-	6	-	-	-	+	-	6	+	-	1
7	Meenakshi	22	F	6	12	1	+	-	5	+	-	4	+	+	8+	+	-	2	+	-	6	-	-	-
8	Sandhya	17	F	12	34	20	+	+	8+	+	+	8+	+	+	8+	+	+	4++	+	+	8+	+	+	6++
9	Jenifer	34	F	4	24	0	+	-	3	+	-	2	+	-	6	+	-	1	+	-	4	+	-	1
10	Thirupathamal	32	F	36	27	2	+	-	6	+	-	4	+	+	8+	-	-	2	+	-	3	+	-	1
11	Gangabavani	19	F	24	27	11	+	+	8+	+	+	8+	+	+	8+	+	++	6++	+	+	8+	+	++	7++
12	Devaki	28	F	24	32	1	+	-	4	+	-	4	+	+	8+	+	-	3	+	-	7	+	-	1
13	Rahima	32	F	18	30	2	+	-	6	+	-	5	+	+	8+	+	-	2	+	-	3	+	-	1
14	Lakshmi	24	F	11	21	3	+	+	8+	+	+	8+	+	+	8+	+	-	-	+	-	6	+	-	1
15	Selvi	26	F	18	32	3	+	-	6	+	-	3	+	+	8+	+	-	1	+	-	6	+	-	1
16	Kanchana	21	F	24	19	0	-	-	-	-	-	-	+	-	6	+	-	2	-	-	6	+	-	1
17	Santhanalakshmi	17	F	3	27	0	+	-	7	+	-	4	+	-	7	+	-	1	+	-	4	+	-	1
18	Karthayee	23	F	12	24	2	+	-	5	+	-	5	+	+	8+	+	-	2	-	-	-	+	-	-
19	Malliga	24	F	24	32	3	+	-	6	+	+	4	+	-	8+	+	-	3	+	-	6	+	-	1
20	Boopathiyamma	31	F	42	26	0	+	-	6	+	-	4	+	-	6	+	-	2	+	-	3	+	-	1

B- BEFORE 1ST PULSE: A- AFTER 8TH PULSE: +: Persistent at 8th pulse; ++: relapsed

SYSTEMIC LUPUS ERYTHEMATOSUS- MASTER CHART cont.

Pt. No	Name	JOINT			Renal		CNS		Others		Anti dsDNA		ANA			ESR		TOTAL COUUNT	
		B	A		B	A	B	A	B	A	B	A	Pattern	B	A	B	A	B	A
1	Ponni	+	-	3	+	-	-	-	-	Pulmn	1 : 1280	1 : 160	R	1: 1280	1: 40	55/120	35/75	4500	5100
2	Krishnamurthi	+	-	4	+	-	-	-	Vasculitis	-	1 : 320	1 : 40	R	1: 80	1:40	80/115	4/10	3800	4100
3	Rekha	+	-	2	-	-	-	-	-	-	1 : 160	1 : 10	R	1: 40	1: 40	3/18	6/14	5600	5300
4	Lakshmi	+	-	1	-	-	-	-	-	-	1 : 40	Negative	H	1: 160	Neg	30/62	9/15	4100	4500
5	Lalitha	+	-	6	-	-	+	-	-	-	1 : 640	1 : 10	R	1: 160	1: 10	44/96	7/15	4800	5200
6	Soundari	-	-	-	-	-	+	+	-	-	1 : 640	1 : 160	S	1: 320	1: 10	37/80	22/41	6700	5800
7	Meenakshi	-	-	-	-	-	-	-	-	-	1 : 40	1 : 10	S	1: 40	1: 10	5/10	7/12	4500	5600
8	Sandhya	+	+	8+	+	+	+	+	Pulm, Vasculitis	Pulm, Vasculitis	1 : 1280	1 : 1280	H	1: 1280	1: 320	65/120	28/52	4100	4200
9	Jenifer	+	-	6	-	-	-	-	-	-	1 : 40	Negative	H	1: 40	1: 10	4/11	5/11	6700	5900
10	Thirupathamal	+	-	5	-	-	-	-	Vasculitis	-	1 : 40	1 : 10	R	1: 40	Neg	12/38	4/12	5400	5800
11	Gangabavani	+	+	7++	+	+	+	+	-	-	1 : 1280	1 : 1280	H	1: 640	1: 160	60/124	24/54	3900	4500
12	Devaki	+	-	4	-	-	-	-	-	-	1 : 160	Negative	S	1: 80	1: 10	30/56	11/18	6100	6900
13	Rahima	+	-	5	-	-	-	-	Vasculitis	-	1 : 160	1 : 10	R	1: 10	1: 10	14/28	8/14	7200	6800
14	Lakshmi	-	-	6	-	-	+	-	-	-	1 : 320	1 : 40	H	1:160	1:10	18/44	3/14	4800	4100
15	Selvi	-	-	-	-	-	-	-	-	-	1 : 40	Negative	R	1:40	Neg	12/28	7/15	6400	6700
16	Kanchana	+	-	-	-	-	-	-	-	-	Negative	Negative	R	1:40	Neg	3/11	4/10	5600	6400
17	Santhanalakshmi	+	-	4	-	-	-	-	-	-	1 : 10	0	H	1: 10	1: 10	11/36	5/10	4500	5200
18	Karthayee	+	-	7	+	+	+	-	Serositis	-	1 : 1280	1 : 160	R	1: 320	1: 40	64/120	20/44	4600	6100
19	Malliga	+	-	4	+	-	-	-	-	-	1 : 640	1 : 10	H	1: 40	1: 10	24/82	5/14	4300	5100
20	Boopathiyamma	+	-	3	+	-	-	-	Vasculitis	-	1 : 1280	1 : 40	H	1: 40	1: 10	37/84	5/18	4600	5300

R- Rim pattern: H- Homogenous: S- Speckled